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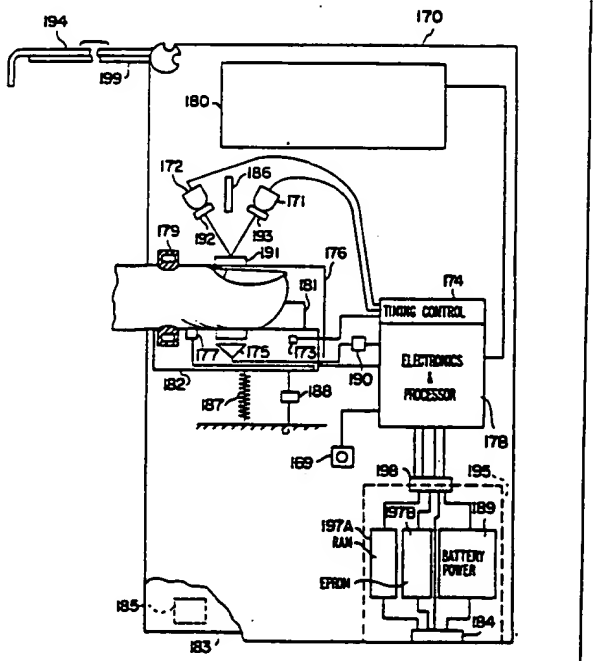
(54) Title: NON-INVASIVE MEASUREMENT OF BLOOD GLUCOSE

(57) Abstract

Near-infrared quantitative analysis instruments (170) non-invasively measure blood glucose by analyzing near-infrared energy following interactance with venous or arterial blood, or transmission through a blood containing body part. A replaceable cartridge (195) stores data unique to an individual patient/user. The analysis instruments (170) are accurate and readily lend themselves to at-home testidiabetics. A method is also disclosed for easily and reliably custom calibrating near-infrared quantitative analysis instruments including obtaining a plurality of blood samples and blood glucose level measurements thereof at a predetermined time interval. These values are entered into the analysis instrument. Near-infrared optical measurements of the individual are simultaneously taken using the analysis instrument at another predetermined time interval. Calibration regression analysis is performed on the data to custom calibrate the analysis instrument which involves linearly interpolating the blood sample glucose measurements with the near-infrared optical recordings.



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NON-INVASIVE MEASUREMENT OF BLOOD GLUCOSE

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to instruments and methods and instrumentation for the non-invasive quantitative measurement of blood analytes. This invention further relates to instruments and methods for the non-invasive quantitative measurement of blood glucose. More particularly, this invention provides a hand-held blood glucose analysis instrument including a replaceable cartridge containing data concerning a particular patient. This invention also relates to a method for providing custom calibration for near-infrared instruments for measurement of blood analytes.

Description of Background Art

Information concerning the chemical composition of blood is widely used to assess the health characteristics of both people and animals. For example, analysis of the glucose content of blood provides an indication of the current status of metabolism. Blood analysis, by the detection of above or below normal levels of various substances, also provides a direct indication of the presence of certain types of diseases and dysfunctions.

The normal method of determining blood chemistry is by removing a sample of blood (e.g. 5-10 ml) and performing one or more standard chemical tests. These types of tests are moderately expensive, require one class of trained technicians to remove the blood and another class of trained technicians to perform the chemical tests. Moreover, the results of the blood tests

often are not available for several hours, and sometimes even several days.

Recently, an alternative type of technology (i.e. self-contained instruments) has been introduced for relatively rapid blood screening of a large number of subjects. These instruments, in general, use a much smaller blood sample (approximately .25 ml) from a "finger poke." This small blood sample is placed on a chemically-treated carrier and entered into the instrument. These instruments normally provide either an individual analysis (e.g., glucose level) or multiple analyses in a few moments. These types of instruments unfortunately are quite costly, e.g., in the range of several thousand dollars.

A third class of blood instrumentation is available for the specific purpose of determining glucose level in people with diabetes. This technology also uses a small sample from a finger poke and the sample is placed on a chemically treated carrier which is inserted into a portable battery operated instrument. In general, these instruments provide a single function, i.e., measurement of glucose. Although these specialized instruments are relatively low cost ($300 or less is typical), the cost of the disposable carrier "stick" must be considered. Since some diabetic patients may require glucose analysis four or more times a day, the cost over a period of a year can become significant.

Current glucose analytical systems require blood to be extracted from the body prior to performing the analysis. This blood withdrawal requirement limits the application of such testing; many people who may be interested in knowing their glucose level are reluctant to have either their finger poked or blood samples removed by hypodermic needle. This reluctance or anxiety in allowing blood sample removal is due to concern over

the possibility of infection, discomfort (pain) and generalized patient fear.

Thus, there is a great need for non-invasive analytical instruments and methods that would provide essentially the same accuracy as conventional blood glucose tests. Moreover, there is a need for a non-invasive low-cost method for measurement of glucose in diabetic patients.

Near-infrared (sometimes referred to herein as simply "near-IR") quantitative analysis is widely used in the field of agriculture for determining chemical compositions within grain, oilseeds, and other agricultural products. As an example, near-IR energy reflected from the surface of finely ground seeds and grain provides information concerning protein and moisture content. For a general introduction to near infrared quantitative analysis, see "An Introduction to Near-Infrared Quantitative Analysis" presented by Robert D. Rosenthal at the 1977 Annual Meeting of the American Association of Cereal Chemists. Near-infrared technology has been extended to allow totally non-destructive measurements by using light transmission through a sample as discussed in "Characteristics of Non-Destructive Near-Infrared Instruments for Grain and Food Products" by Robert D. Rosenthal, presented at the 1986 Meeting at the Japan Food Science Institute. Although this transmission approach avoids the need to finely grind the sample, it is not suited for use where access to two opposite surfaces is not available.

One example of this transmission approach is provided in U. S. Patent No. 4,621,643 (New, Jr. et al., 1986) which relates to an optical oximeter apparatus for determining pulse rate and degree of arterial oxygen saturation. Light energy is passed through an appendage of the body, e.g. a finger, and strikes a detector

positioned on a side of the appendage opposite from the light source. Pulse rate and saturated oxygen are calculated from coefficients of extinction of light at the selected wavelengths.

Another approach to near-infrared quantitative analysis, using near-infrared interactance, was developed for non-invasively measuring body fat content. This approach is described in "A New Approach for the Estimation of Body Composition: Infrared Interactance," Joan M. Conway et al., The American Journal of Clinical Nutrition, 40: Dec. 1984, pages 1123-1230. In this non-invasive technique, a small optical probe that allows optical energy to enter the arm is placed on the biceps. The percent body fat of the entire body is determined by measuring the spectrum change of the energy returned from an area adjacent the light entry point.

A limitation of the near-infrared blood glucose measurement instruments is that each may be required to be custom calibrated for each individual user. The need for individual custom calibration results from the different combination of water level, fat level and protein level in various individuals which causes variations in energy absorption. Since the amount of glucose in the body is less than one-thousandth of these other constituents, variations of these constituents which exist between people may make a universal calibration unlikely.

The current approach for custom calibrating near-infrared blood glucose measurement instruments is to use an in vitro technique that requires removing blood from the subject and having an automatic instrument measure the glucose level of that blood. Such in vitro measurements are typically made with either the commercially available Biostator or the experimental Kowarski Continuous Monitor. Each of the above

instruments requires a catheter to be inserted into the subject and blood withdrawn over a one-to two-hour period. Although such an approach is feasible, it places a significant new burden on the doctor and the medical facility to have enough time, room and equipment to be able to calibrate instruments in this fashion.

Thus, there is a great need for a technique which allows an individual user to easily and reliably custom calibrate the near-infrared instrument.

SUMMARY OF THE INVENTION

In accordance with the present invention, a near-infrared quantitative analysis instrument for measuring blood glucose comprises means for introducing near-IR energy into blood present in a body part of a subject, means for detecting near-IR energy emerging from the subject, means for converting an electrical signal corresponding to the detected energy into a readout indicative of the quantity of glucose present in the blood of the subject, and means for positioning the introducing means and detecting means adjacent to the body part of the subject.

The present invention also provides methods for the near-infrared quantitative analysis of blood glucose, these methods including the steps of introducing near-IR energy into the blood within a body part of a subject, detecting near-IR energy emerging from the subject, the detector providing an electrical signal upon detecting said emerged energy, and processing the electrical signal to provide a second signal indicative of the amount of glucose present in the blood. Some of these inventive methods utilize the principle of near-IR transmission while others utilize the principle of near-IR interactance.

In accordance with another aspect of the present invention, a near-infrared quantitative analysis instrument for measuring blood glucose comprises means for introducing near-IR energy into blood present in a blood vessel, means for detecting near-IR energy following interactance of the same with the blood, and means for positioning the introducing means and detecting means over a blood vessel of the subject.

This aspect of the invention further relates to methods wherein near-IR energy is introduced into a vein or artery of a subject and interacts with blood glucose, the near-IR energy emerging from the subject is detected by a detector which provides an electrical signal, and the signal is processed to provide a readout indicative of the amount of glucose in the blood.

This aspect of the invention also relates to means and methods for marking a position over a vein or artery of a subject and then aligning a near-IR analysis instrument with the markings to accurately position the instrument.

Another aspect of the invention relates to an apparatus for measuring blood glucose via near-IR transmission through a blood-containing body part, the apparatus including means for introducing near-IR energy into one side of a body part, means for detecting near-IR energy emerging from an opposite side of the body part and means for positioning the near-IR introducing and detecting means on opposite sides of the body part.

This aspect of the invention also relates to methods for measuring blood glucose via near-IR transmission including the steps of introducing near-IR energy into one side of a blood-containing body part, detecting near-IR energy emerging from an opposite side of the body part and calculating blood glucose content.

In accordance with another aspect of the invention, a near-infrared quantitative analysis instrument comprises means for m asuring blood glucose via near-IR transmission through a blood-containing body part, the instrument including means for introducing near-IR energy into one side of a body part, means for detecting near-IR energy emerging from an opposite side of the body part and means for positioning the near-IR introducing and detecting means on opposite sides of the body part.

The analysis instrument is comprised of a lightweight, hand-held instrument including a base housing unit and a replaceable cartridge means which engages the base unit. The replaceable cartridge includes a memory device for storing data associated with a particular patient and the particular base unit, and may also include the power source for the analysis instrument. The data stored in the replaceable cartridge may include a series of glucose readings and calibration constants custom calibrated for the individual user.

In accordance with another aspect of the present invention, a low-cost method and means for providing custom calibration for near-infrared instruments for measurement of blood glucose comprises obtaining a plurality of blood samples from an individual at a predetermined time interval and for a predetermined period of time. Blood glucose measurements for each blood sample are obtained and are entered into the near-infrared instrument. Non-invasive near-infrared optical absorption measurements are concomitantly taken through a body part of the individual at a second predetermined time interval and are recorded in the analysis instrument. Calibration regression analysis is then performed utilizing means for linearly interpolating the blood sample glucose measurements with the near-infrared

optical measurements to custom calibrate the near-infrared instrument for the individual.

Another aspect of the present invention relates to a method of compensating for calibration errors resulting from changes in an individual's skin temperature. This technique involves producing a change in the individual's skin temperature while obtaining the non-invasive near-infrared blood glucose measurements. The individual's skin temperature is thereby forced to have a meaningful temperature range during the calibration process.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a partially schematic elevational view of a near-infrared quantitative blood analysis instrument to which the present invention pertains;

FIGS. 2A and 2B are partially schematic elevational views of alternate embodiments of near-infrared quantitative analysis instruments;

FIG. 3 is an elevational view of a location device for use with the instrument shown in FIG. 1;

FIG. 4 illustrates one embodiment for practicing the inventive method;

FIGS. 5A and 5B illustrate two known configurations for interposing filters in a light path;

FIG. 6 is a plot of log (1/I) versus wavelength;

FIG. 7 illustrates a wavelength search study via a plot of correlation coefficient versus wavelength;

FIGS. 8 and 9 illustrate plots of correlation coefficient versus wavelength for first derivative equations;

FIGS. 10 and 11 illustrate plots of correlation coefficient versus wavelength for second derivative equations;

FIG. 12 is a plot of log (1/I) versus wavelength which illustrates near-infrared energy absorption by water;

FIG. 13 is a plot of log (1/I) versus wavelength illustrating two measurement wavelengths which straddle a water band;

FIG. 14 illustrates that energy absorption by water varies with temperature;

FIG. 15 illustrates a difference spectra of glucose absorption of near-infrared energy in the body;

FIG. 16 is a plot of correlation versus wavelength illustrating the effect of a temperature term in the linear regression equation;

FIG. 17 is a plot of mid-wavelength and correlation versus gap between wavelength "A" and "B";

FIGS. 18A-D illustrate classes of peaks which correspond to the shape of a correlation versus wavelength curve;

FIG. 19 illustrates a non-invasive glucose measurement instrument according to another embodiment of the present invention;

FIG. 20 illustrates a non-invasive glucose measurement instrument according to another embodiment of the present invention;

FIG. 21 illustrates a hand-held non-invasive glucose measurement instrument according to another embodiment of the present invention;

FIG. 22 illustrates a bottom view of the non-invasive glucose measurement instrument of FIG. 21;

FIG. 23 shows a schematic representation of a replaceable cartridge according to the present invention;

FIGS. 24A-D are plots of official laboratory glucose values versus near-IR instrument glucose values illustrating potential extrapolation errors;

FIG. 25A and 25B show different sized finger inserts for the glucose measurement instrument;

FIG. 26 shows an interactance type non-invasive glucose measurement instrument according to one embodiment of the present invention;

FIG. 27 shows a side view of the interactance instrument of FIG. 26.

FIG. 28 is a flow diagram illustrating the method for custom calibrating a near-infrared analysis instrument for the measurement of blood glucose levels according to the present invention;

FIG. 29 shows a schematic representation of custom calibration instrumentation according to another aspect of the present invention;

FIG. 30 shows a schematic representation of custom calibration instrumentation according to another aspect of the present invention; and

FIG. 31 is a graph showing near-infrared energy absorption by water as a function of temperature.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with one embodiment, the invention uses the principle of light interactance to measure blood glucose level non-invasively by locating an optical transmitter and a detector on the skin surface near either an artery or a vein. Alternatively, the invention uses the principle of light transmission through a portion of the body that has relatively uniform profusion of blood in order to measure blood glucose non-invasively.

In general, the arteries and veins of the human body are buried deep in the body to protect them from possible harm. However, in certain locations of the body, these blood-carrying vessels are close to the skin surface. This is particularly true for veins. Some examples of

such locations are at the crease of the elbow, the wrist, the back of the hand, and the bridge of the nose. Since the concentration of glucose is relatively constant in both the veins and arteries, valid measurements can be obtained in either. However, because veins are generally closer to the skin's surface, they usually are the better candidate for non-invasive measurements.

The finger-tip is another site particularly well suited for performing blood measurements with near-IR light. The blood supply is distributed within the finger tip and, thus, small variations in the placement of a near-IR emitter or detector will not have a profound effect on the measurement results.

According to one embodiment of the invention utilizing near-IR interactance analysis techniques, near-IR light energy at bandwidths centering on one or more wavelengths of interest is passed through the skin and connective tissues and into a blood vessel of a subject. A portion of the energy re-emerges from the blood vessel of the test subject and is detected by a detector. Following amplification of the detector-generated signal, the amplified output is processed into an output signal indicating the amount of glucose in the subject's blood. The output signal drives a display device for providing a visual display of blood glucose content.

According to another embodiment of the invention utilizing near-IR transmission analysis techniques, near-IR light energy at bandwidths centering on one or more wavelengths of interest is transmitted through a blood-containing portion of the body of a test subject. The near-IR energy emerges from the test subject, generally opposite from the near-IR source, and is detected by a detector. Following amplification of the detector-generated signal, the amplified output is processed into

an output signal indicating the amount of glucose in the subject's blood.

In one embodiment utilizing near-IR interactance, the entire analytical instrument, including near-infrared source, transmitter, detector, amplifier, data processing circuitry and readout is contained within a lightweight hand-held unit. See Fig. 1. Infrared emitting diodes (IREDs) disposed in one chamber of the unit are focused to transmit near-IR energy of preselected wavelength(s) to, e.g., a prominent vein of the wrist. The near-IR energy interacts with the constituents of the venous blood and is re-emitted from the vein. A detector housed within a second chamber of the unit is disposed along the vein a distance (ℓ) from the emitter and collects this energy. The detected signal is amplified and data processed into a signal indicative of the amount of glucose in the blood. This signal is then fed to a readout device (preferably a digital readout) for recordation by a technician or direct analysis by a physician or the subject.

Other near-IR apparatus, such as the optical probe and associated instrumentation described in U.S. Patent No. 4,633,087 (Rosenthal), are useful in the practice of the present methods in which near-IR interactance is used to quantitatively measure blood glucose levels.

This embodiment can utilize a location device specially adapted to permit the user to locate the interactance instrument discussed above accurately along a vein. The location device permits the skin to be marked to ensure that repeated measurements are taken from the same location.

In the lightweight, hand-held interactance analysis instrument 10 illustrated in Fig. 1, included is one or more means for providing at least one point source of near-infrared energy of a predetermined bandwidth of

interest which is positioned within a first chamber 30 of the instrument 10. The near-infrared point source means is positioned so that near-infrared energy being emitted from the point source means will be focused by lens 12 through window 14 and onto the skin of the test subject. The near-infrared point source means may comprise one or a plurality of infrared emitting diodes (IREDs). Two such IREDs 16, 16' are visible in the embodiment illustrated in Fig. 1. In other embodiments employing a plurality of IREDs, three, four or more IREDs may be utilized as the point source means.

In lieu of laborious characterization and sorting of each IRED, narrow bandpass optical filters (as shown schematically in Fig. 1) can be provided between the infrared emitting diodes and the lens 12. According to this embodiment, a filter 23 is positioned between each IRED and lens 12 for filtering near infrared radiation exiting each IRED and thereby allowing a narrow band of near-infrared radiation of predetermined wavelength to pass through the filter and lens 12. Utilization of narrow bandpass optical filters provides for specific wavelength selection independent of the center wavelengths of the particular infrared emitting diodes being used. Measurements can be taken inside the half power bandwidth of the IREDs, or alternatively, outside the half power bandwidth of the IREDs as disclosed in U.S. Patent No. 4,286,327. Figs. 5A and 5B illustrate two other known configurations for interposing filters 23' and 23", respectively, in a light path. The light source in Figs. 5A and 5B can be either a light bulb 17 or 17', respectively, or one or more IREDs.

An optical detector, illustrated schematically in Fig. 1 and designated by reference numeral 28, is disposed within a lower end portion 42 of a second chamber 40 in case 20. Inner wall 22 is positioned

between detector 28 and illumination section 30, thereby providing an optically-isolating mask which prevents near infrared radiation from the point source means and/or lens 12 from impinging directly on detector 28. The near-infrared optical detector 28 generates an electrical signal when near-infrared radiation is detected thereby.

The optical detector 28 is connected to the input of an electrical signal amplifier 32 by suitable electrical conducting means 33. Amplifier 32 may be an inexpensive integrated circuit (IC) signal amplifier, and amplifies the signals generated when near-IR energy strikes detector 28. The output of amplifier 32 is fed to a controller/data processor and display driver 34 which provides a signal to readout device 36. The readout device 36 may have a digital display for directly displaying the amount of glucose present in the subject's blood.

The embodiment of Fig. 1 includes an optical filter 29 for shielding all but the desired near-IR energy from detector 28. Filter 29 and window 14 are positioned for direct contact with the skin of the test subject. An optically clear window can be employed in lieu of filter 29, if desired, and in lieu of the window opening 14.

As noted earlier, the embodiment illustrated in Fig. 1 utilizes the principle of near-IR interactance for quantitative analysis. In interactance, light from a source is shielded by an opaque member from a detector so that only light that has interacted with the subject is detected.

In use, the analysis instrument 10 is positioned so that its flat bottom surface rests on the skin directly above the prominent vein of the wrist of a test subject. Light at the selected wavelengths emerging from the instrument interacts with venous blood of the subject and

is detected by detector 28. Detector 28 generates an electrical signal which is processed as described above.

Accurate analysis is facilitated when the user locates the transmitter and detector filter (or window) directly over the prominent vein of the wrist. The location device illustrated in Figure 3 simplifies this procedure. The device 50 is constructed of, e.g., a plastic material and has an overall length L equal to the length L of the analysis instrument 10 of Figure 1. Two holes 51 are present in the device and are located in the same relation as 14 and 29 in Figure 1, on midline 52, a distance ℓ apart corresponding to the distance ℓ of Figure 1. The holes 51 permit observation of the prominent vein. When the device is placed on the wrist and the vein is centered in each hole 51, the wrist is marked (e.g. with a felt-tipped pen) at notches 53. The location device is then removed and replaced by the analysis instrument 10 with assurance that the instrument is properly located over the vein.

An alternate procedure for practicing the inventive method is accomplished by the use of fiber optic light probes as seen in Figure 4. These probes are connected with a near-IR analysis instrument such as the commercially available TREBOR-70 scanning spectrophotometer which has been adapted to process a signal for glucose analysis. A probe 60 is placed over the prominent vein and transmits near-IR energy of the desired wavelength(s). The near-IR energy interacts with the blood constituents and is collected by a second probe 62 placed over the vein a short distance ℓ from first probe 60. A detector associated with the analytical instrument provides an electrical signal which is processed, as described above, to reveal quantitative information concerning blood glucose.

It has been found that accurate quantitative analysis of blood glucose levels can be made at a variety of wavelengths with both interactanc and transmittance technologies. In presently preferred embodiments illustrated in Figures 2A and 2B, near-IR light energy is transmitted through the finger of the test subject and then detected by an optical detector. As in the above described embodiments, a combination of measurement wavelengths is selected which emphasizes the glucose absorption and removes the effect of interfering absorption, for example, due to water, fat and protein.

In the embodiment shown in Figure 2A, a near-IR probe 100 is adapted to be placed over the finger F of a test subject and in this particular embodiment includes a point source means of near-IR light energy comprised of at least two IREDs 116 disposed within an upper flange 110. Each IRED is paired with a narrow bandpass optical filter 123 and is optically isolated via opaque light baffle 119. The inwardly-facing surface of flange 110 is provided with an optional optically clear window 114 for placement against the subject's finger.

Upper flange 110 is hinged about shaft 111 to lower flange 120, and a spring 112 serves to maintain the flanges in a closed position. An optical detector 128 is disposed in lower flange 120 opposite the near-IR source 116. The detector is disposed behind an optional window 129 which can be constructed of a material which is either optically clear or which excludes interfering light yet permits the desired near-IR light to pass. A finger stop 103 helps place and maintain the subject's finger in its proper position within the probe 100. Each of the flanges is provided with light-shielding barriers 113 (shown in phantom in Figure 2A) to block ambient light from entering the probe.

In this embodiment the IREDs are pulsed, i.e., energized in sequence, so that the detector 128 receives light transmitted from only one of the IREDs at any one time. This pulsed IRED technology is described in U.S. Patent No. 4,286,327 which is incorporated herein by reference. In other similar embodiments a group of IREDs (and optional narrow bandpass filters) with substantially identical center wavelength output can be pulsed.

Probe 100 is an electrical connection with a processor unit which is schematically illustrated in Figure 2A. The processor unit houses a power source, signal amplifying, data processing and display circuitry as described in connection with the embodiment of Figure 1 and standard in near-IR analysis instrumentation.

An alternate embodiment is seen in Figure 2B. Here, probe 110 includes a single constant output IRED 116 installed behind an optional window 129. Light transmitted through the finger is gathered by optical funnel 112A, which is constructed of a transparent or translucent material, and detected by multiple detectors 128. The detectors are optically isolated from one another by opaque light baffle 119. Each detector is paired with a narrow bandpass optical filter 123 and thus is set up to detect only light within the narrow wavelength range of its filter.

Near-IR point source means 116 can consist of one or more IREDs of known bandwidth and center frequency output or, as described above, can include a narrow bandpass optical filter within the light path to provide for the detection of only those wavelengths which are of interest. Multiple wavelengths can be utilized in transmission analysis and can be generated via multiple IREDs provided they are consecutively illuminated. Another approach is to use a single IRED with multiple bandpass filters which are mechanically moved through the

light path as seen in Figures 5A and 5B. A third approach uses a single or group of IREDs capable of emitting a plurality of desired wavelengths with the use of multiple optical filters, each filter being associated with a respective detector. Single IREDs which emit two, three or four narrow bandwidths are commercially available.

In use, the finger of the test subject is inserted between the flanges 110 of the probe 100. Near-IR light energy is emitted by the point source means, is transmitted through the finger and is detected by optical detector 128. The electrical signals produced by the detectors are transmitted via line 130 to a controller/processor unit 150 where the signal is amplified and data processed using a suitable algorithm as described below. Blood glucose level is displayed on a readout device which preferably includes a digital display.

Accurate measurements of the concentration of blood glucose can be made using near-IR quantitative analysis algorithms which have only a single variable term, such as the following:

Approximated First Derivative Algorithm

$$C = K_o + K_1 [\log 1/I_G - \log 1/I_H]$$

Approximated Second Derivative Algorithm

$$C = K_o + K_1 [\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]$$

Normalized First Derivative Algorithm

$$C = K_o + K_1 \frac{[\log 1/I_G - \log 1/I_H]}{[\log 1/I_I - \log 1/I_J]}$$

Normalized Second Derivative Algorithm

$$C = K_o + K_1 \frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]}$$

where C denotes concentration of glucose present in the blood, K_0 is the intercept constant, K_1 is the line slope of the variable term, and the log 1/I terms each represent an Optical Density (O.D.) value at a particular wavelength. In Fig. 6, an example of an overall absorbance curve for a test subject is shown, wherein log 1/I (O.D.) values for the above algorithms are plotted. In Fig. 6, optical energy is absorbed at wavelength B proportional to the constituent being measured, and optical energy is absorbed at wavelength E proportional to the total substance being measured. Points 151 and 152 are first derivative midpoints. The distance between, for example, wavelength G and wavelength H is referred to herein as the "gap" between two wavelengths. It has been found that a plurality of wavelength pairs, all centered on the same wavelength, can be used in the above algorithms. These algorithms are easily programmed into suitable microprocessor circuitry by those skilled in the art. The use of these single variable term equations is highly desirable because it allows simplified instrument calibration, thereby allowing the production of low-cost instruments.

The intercept constant K_o and the slope constant K_1 are determined by individually calibrating each unit.

Another class of usable near-IR standard algorithms involves the use of multiple regression terms. Such terms can be individual log 1/I terms or can be a multiple number of first or second derivative terms with or without a normalizing denominator. Such multiple terms may provide additional accuracy, but introduce

higher calibration expense which results in a more expensive instrument.

Data on a plurality of physical parameters of th test subject can also be utilized in conjunction with multiple wavelength measurement of near-infrared interactance, as in prior U.S. Patent No. 4,633,087, to improve the accuracy of the present blood glucose measurements.

Selection of combinations of wavelengths which emphasize glucose absorption and remove possible interfering absorptions can be performed by computer search studies. In general, a suitable combination of wavelengths will include at least one wavelength which is sensitive to blood glucose, and at least one wavelength which is insensitive to blood glucose (reference wavelength). The following examples show results of wavelength search studies, which are provided herein for illustrative purposes only, and are not to be construed in a limiting sense.

Example I

Figure 7 presents correlation coefficient versus wavelength data from a search study utilizing an approximated first derivative algorithm as defined above, and illustrates that the use of the wavelength pair of 980 ± (plus and minus) 35 nm provides a high correlation between blood glucose and absorption of near-IR energy at those two wavelengths. Figure 7 utilizes the above approximated first derivative algorithm, wherein G and H are as shown in Figure 6, and equal to 945 nm and 1015 nm, respectively. Thus, in this example, the "gap" is 70 nm (1015 nm - 945 nm). The number of samples tested was 30 in this case. The value of K_o in the approximated first derivative algorithm is 196.9 and for K_1 is 4,802.6. In this case, the standard deviation was 13.54, with a correlation of +0.948. Reference numeral 154 of

Figure 7 indicates a range of candidates for wavelength H with a "gap" equal to 70 nm and a "smoothing" factor of 41. "Smoothing" is the modification of data derived from a scanning spectrophotometer in order to simulate the results which would be obtained at the half power bandwidth of optical filters. "Smoothing" involves taking log 1/I data at an equal number of wavelengths above and below each wavelength of interest and averaging the results. Thus, with a "smoothing" value of 41, data is taken at 20 wavelengths above and 20 wavelengths below the bandwidth of interest, in addition to each wavelength of interest. An example of one embodiment of the invention uses IREDs which provide near-IR energy at two frequencies which are, respectively, equidistant above and below approximately 980 nm, i.e., they can be represented by the formula 980 ± x nm. The value of x is not unduly critical so long as the two frequencies are centered on approximately 980 nm. A suitable value for x can be, for example, a number from 10 to 40.

Example II

Figure 8 shows that a suitable wavelength for a numerator in the above normalized first derivative algorithm is approximately 1013 nm (i.e., 980 nm + 35 nm) wherein K_o = 296.8, K_1 = -175.6, "gap" G-H: 70 nm, wavelength J: 915 nm, "gap" I-J:20 nm, standard deviation = 12.21 and correlation = - 0.958 (30 samples).

Example III

Figure 9 shows that there are many wavelength regions that can provide midpoint wavelengths for use in the denominator of the above normalized first derivative algorithm when the numerator utilizes 980 ± 35 nm wavelengths, wherein K_o, K_1, "gap" G-H, gap I-J, standard deviation, correlation and sample size are the same as in Example II and Figure 8, and wherein wavelength H is 1013 nm. Examples of such wavelength regions are seen to be

from 610 to 660 nm, from 910 to 980 nm and from 990 to 1080 nm.

Example IV and V

Figures 10 and 11 illustrate optimum center wavelengths for use in the normalized second derivative algorithm described above. Figure 10 is a plot of correlation coefficient versus wavelength which shows that a suitable numerator center frequency is approximately 1020 nm, wherein in the above normalized second derivative algorithm, K_o = 205,856, K_1 = 356.457, "gap" A-B and B-C = to 53 nm, wavelength E: 850 nm, "gap" D-E and E-F = to 68 nm and standard deviation = 20.44 (47 samples). Figure 11 shows that a denominator center frequency of about 850 nm is suitable, wherein K_o, K_1, "gap" A-B and B-C, "gap" D-E and E-F, standard deviation, and sample size are as in Figure 10, and wherein wavelength B is 1020 nm.

The accuracy of the preferred near-IR transmission embodiments shown in Figs. 2A and 2B can be further improved by altering the algorithm to include finger thickness as a parameter. According to Lambert's law, energy absorption is approximately proportional to the square of the thickness of the object. The thickness of the test subject's finger can be quantified by installing a potentiometer 140 between the flanges of the probe 100 as seen in Figures 2A and 2B. The output of the potentiometer, which is in electrical connection with the data processing circuitry, is indicative of finger thickness. A non-linear potentiometer can approximate the T^2 value via its output alone so that a separate squaring calculation step is not necessarily required.

Selection of suitable combinations of measurement wavelengths can take into account the identification and removal of possible interfering absorptions, such as due to water. Figure 12 illustrates that water is one of the

strongest absorbers of near-IR energy. The effect of this inherent strong absorption is magnified by the very high water content in the human body (i.e., approximately 60% for the average person). Thus, measurements in the near-infrared must be performed with care to avoid being distorted due to slight changes in body water caused by either dehydration (e.g., perspiration) or due to excessive intake of fluids.

This care is particularly critical when trying to measure blood glucose. This is because of the extremely low concentration of glucose level in the blood (average of approximately 100 milligrams per deciliter).

The wavelength search studies discussed above illustrate that where the mid-wavelength between the two measurement wavelengths would be approximately at the center of a water "dead band" (i.e., minimal interference due to water), good measurement has been provided (see Figure 7). The reason for this is that these two measurement wavelengths straddle the water "dead band," and thereby minimize errors due to the change in water content. Figure 13 illustrates that the two measurement wavelengths which straddle the water band correspond to the wavelength pair in Figure 7 which provides a high correlation between blood glucose and absorption of near-IR energy.

However, Figure 14 illustrates the well-known phenomenon that the water absorption curve varies with change in temperature. Since temperature at different extremities on the body can vary for a variety of reasons, illness or ingestion of cold or hot fluids/foods, the potential for error in glucose measurement made where the wavelength pair straddles the water band may become excessive.

To overcome this potential temperature limitation, two regions of the spectrum have been discovered that

appear to be well suited for measurement of blood glucose. These are indicated as Region "J" and Region "K" in Figure 12 for the standard near-IR absorption curve for water. In Region "J", the water absorption curve reaches a minimum near 1070 nm. In this region, changes in water concentration would have the least effect of any place in the longer wavelength spectrum.

Figure 15 illustrates the effective spectra of glucose in the human body. This spectra was developed by subtracting two spectra obtained by transmitting optical energy at 1 nm intervals between 600 to 1100 nanometers through the distal portion of the index finger. The two scans were made approximately one hour apart during which time the subject drank a concentrated solution of dextrose, thereby raising the blood glucose level. Thus, this difference in spectra in Figure 15 is primarily due to glucose.

As shown in this figure, there is a broad absorption due to glucose that occurs between 850 and 900 nm as well as another one that occurs at approximately 1050 nm. Although other absorptions are occurring, they are not as well defined.

The glucose absorption that occurs at approximately 1050 nm causes a negative slope between approximately 1070 to 1100 nm (see Figure 12, Region "J"). This negative slope is measured by using two log 1/I measurements, for example, one at approximately 1070 nm and the other one at approximately 1090, and coincides favorably with the nadir point on water absorption curve (i.e., Region "J", Figure 12). Thus, a change in body water level would have minimal effect on the glucose reading in this area.

As stated above, one of the parameters affecting near-infrared accuracy is change in temperature of the subject being measured. Although there appears to be

little actual relationship between finger temperature and glucose level, it has been discovered that by adding a temperature term to the regression equation, a significant improvement in correlation coefficient occurs. The temperature term can be added to any of the near-IR quantitative analysis algorithms identified as providing accurate measurements of concentration of blood glucose, such as the following:

$$C = K_o + K_1 [\log 1/I_A - \log 1/I_B] + K_2T_s$$

where C denotes concentration of glucose present in the blood, K_o is the intercept constant, K_1 is the line slope of the variable term, K_2 is a calibration constant, the log 1/I terms each represent an Optical Density (O.D.) value at a particular wavelength and T_s represents the local surface temperature of the body where the optical reading is being made. The temperature term T_s can also be added to the algorithms for three, four or six wavelengths described above.

Figure 16 illustrates the improved correlation coefficients obtained in the Region "J" band using the temperature term T_s in the linear regression equation. Although the correlation in Region "J", approximately 1080 nm, is not the highest of any wavelength, it is of a level usable for a commercial instrument, particularly if consideration is given to potential errors introduced due to change in body water level.

In addition to the Region "J" band, the Region "K" band provides a unique measurement candidate for glucose. Figure 12 shows that the water curve has no significant slope from 780 nm to 810 nm (Region "K"). This water "dead band" provides a good wavelength region to measure glucose, as shown by the relatively steep slope of glucose in this region (see Figure 15).

Figure 17 further demonstrates the uniqueness of this Region "K". It shows that the "mid-point" wavelength (i.e., the wavelength halfway between wavelength "A" and wavelength "B") remains essentially constant independent of gap size. This is due to the "dead band" (i.e., no interference due to water). The importance of this Region "K" is further demonstrated by the fact that the correlation coefficient remains high (between 0.94 and 0.95) independent of gap size.

Another parameter affecting near-infrared analysis accuracy is ambient temperature change within the measurement instrument. It is known that the output of silicon optical detectors (the detector of choice in the spectrum regions of 600 to 1100 nm) is extremely sensitive to temperature changes. Thus, varying the "room temperature" could have negative effect on measurement reliability. By adding a third term to the regression equation, i.e., an ambient temperature term, a significant improvement in the correlation coefficient occurs. The ambient temperature term can be added to any of the near-IR quantitative analysis algorithms identified above, such as the following:

$$C = K_o + K_1 [\log 1/I_A - 2*\log 1/I_B] + K_2T_S + K_3T_A$$

wherein each term described above is the same, K_3 is a calibration constant and T_A represents the ambient temperature within the measurement instrument. The ambient temperature term can also be added to the algorithms for three, four or six wavelengths as described above.

In a preferred embodiment, a thermistor is used to measure the instrument's ambient temperature. Although alternative means could be used, a thermistor is the most practical solution for a battery powered instrument.

Accurate measurements of the concentration of blood glucose can be made using any suitable algorithm described above utilizing either two, four or six wavelengths. The two-wavelength model provides the lowest-cost instrument since only two optical measurements need be made. The applicability of the two-wavelength model has been verified by repeatedly testing a group of diverse people, such as those of different racial origins, sex, body fat and those without a history of diabetes. These tests demonstrated high correlation coefficients obtained (e.g., typical correlation coefficients exceed 0.93). Further, tests indicated that wavelengths "A" and "B" which provided the highest correlation were substantially different for each person.

This "wavelength uniqueness" for each person directly results from the individual's organic body composition. The human body is primarily composed of water (55% to 70%), fat (5% to 40%), and protein (5% to 15%). These three constituents add up to more than 95% of the total body composition. Since water, fat and protein all have strong near-IR absorption bands, the measurement of glucose (concentration of less than 0.1% of the body) must be made at wavelengths that have minimum interference by these major near-IR absorptions.

Since each individual has a different relative body composition, the minimum interference points where glucose can be measured differs greatly between individuals. In some instances, this change in wavelength can be as much as 50 nm. Tables I and II reproduced below illustrate this difference. The tables show the correlation coefficient versus measurement wavelength for three different individuals. A constant difference between A and B of 10 nm was retained for the measurements. As shown in Table I, Subject A's optimum "B value" was at 820 nm, where Subject B's optimum "B

value" was at 790 nm, and Subject C's optimum "B value" was at 840 nm.

Table I
FIGURE 18A
Two Wavelength Model
For Halfpower Bandwidth = 15nm

Person	R Correlation	"B" nm	GAP (A-B)
A	.92	790	10
A	.95	820	10
A	.90	840	10
B	.93	790	10
B	.88	820	10
B	Low	840	10
C	Low	720	10
C	.88	820	10
C	.97	840	10

Table II
FIGURE 18B
Two Wavelength Model
For Halfpower Bandwidth = 60nm

R Correlation	"B" nm	GAP (A-B)
.93	790	10
.93	820	10
.91	840	10
.92	790	10
.89	820	10
.84	840	10
Low	790	10
.84	820	10
.86	840	10

The Table I measurements were made using a near-IR source having an optical half-power band width of approximately 15 nm. This half-power band width is commonly used for near-infrared measurements and it can be provided by placing a narrow bandpass optical filter in front of an infrared emitting diode.

Table II illustrates the same data as Table I except for the use of a very wide half-power band width. The half-power band width shown in Table II is equivalent to that provided by an infrared emitting diode without any optical filter (approximately 60 nm). As shown in Table II, there is an accuracy penalty incurred by using these wide band widths. However, with this approach the production of a lower-cost instrument becomes possible because the optical filters can be omitted. Further, it is recognized that, in some cases, this penalty in accuracy would be acceptable.

In the algorithms provided above, the two temperature terms T_S and T_A are not optical variables in that they can be measured by ind pendent thermistors. For this reason, the constants K_2 and K_3 may not vary between instruments.

According to one embodiment of the present invention, a non-invasive blood glucose instrument is constructed which provides an accurate blood glucose level measurement correcting for inaccuracies resulting from each person's "wavelength uniqueness." In the lightweight, hand-held analysis instrument 200 illustrated in Figure 19, included is a means for providing at least one point source of near infrared energy. The near-infrared point source means is positioned so that near-infrared energy being emitted from the point source means will be focused by a lens 212 through window 214 and onto the skin of the test subject. The near-infrared energy emerging from the test subject will travel through window 215 and be detected by detector 228. Detector 228 is electrically connected to controller/processor 250 which calculates the test subject's blood glucose level. In one embodiment of the present invention, also illustrated in Figure 19, the blood glucose measurement instrument 200 is constructed having a first section 210 and a second section 220 pivotally connected together by hinge 211. Spring 212 is connected to first section 210 and second section 220 and facilitates securing the instrument against the test subject's skin, thereby substantially shielding interfering ambient light from detector 228.

In a preferred embodiment, the near infrared point source means may comprise six IREDs 216 (Figure 19 shows only two). The center wavelength of each IRED can be separated by a constant wavelength, for example, an IRED with a center wavelength at 790 nm, the next at 800 nm,

etc. (i.e., center wavelengths from 790 nm to 850 nm). The use of IREDs as a light source allows a simple, low-cost instrument to be d veloped. Also, this instrument could contain just one IRED and utilize the configurations in Figures 5A and 5B for interposing optical filters 23' and 23", respectively, in the light path.

In the embodiment of the present invention utilizing a plurality of IREDs, each IRED is sequentially pulsed. As illustrated in Figure 19, microprocessor 250 is used to sequentially pulse each IRED. Microprocessor 250 can also be used to custom calibrate the instrument to a specific individual. This is accomplished by measuring the person at a time of low glucose level such as after an overnight fast. The person then increases his glucose concentration by, for example, drinking a dextrose solution, and is again measured. The microprocessor can be used to determine which two IREDs provide the maximum difference, and then use those IREDs in subsequent glucose measurements for that individual.

However, if better accuracy is required, optical filters could be used with the IREDs. In such a case, a "filter tray" containing a plurality of interchangeable optical filters could be made available to, for example, a medical professional. The medical professional would have a master instrument that can be used in conjunction with glucose tolerance test. This master instrument would be used to define the optimum wavelength for a specific individual. Moreover, it would define the instrument's calibration constants for that individual as well.

The medical professional could then place the correct optical filters that correspond to what was found on the master instrument into a small portable home instrument. These optical filters would be installed using the

"filter tray" discussed above, thereby customizing a home instrument for that specific individual. Likewise, the calibration constants will also be entered into the instrument by the medical professional.

In another embodiment of the present invention, the four-wavelength model enables accurate glucose measurement testing and has as a major advantage that the wavelengths would not have to be varied for each individual tested. One set of wavelengths is applicable for all people.

Table III reproduced below presents a comprehensive listing of candidate wavelength combinations for this model. This data (as well as the six-wavelength model candidates) was derived from actual tests on three separate individuals, two of whom were diabetics. These tests included a minimum of 200 separate measurements on each person while their blood glucose varied considerably by undergoing glucose tolerance tests. Because of the diversity of these individuals, it is believed that the data shown is reasonably representative of the general population.

Table III

DELTA OD/DELTA OD; ALL REASONABLE CANDIDATES
(R > .8)

Criteria: Must be OK on 3 People; "R_{min}" is lowest correlation coefficient of the lowest person.

NUM "B"	GAP (A-B)	Class	Region	DEN "E"	GAP (D-E)	R_{min}
705	10	4	D	650	30	.91
711	20	4	D	650	10	.87
1091	20	3	A	650	20	.85
1087	20	4	A	660	10	.84
1090	20	3	A	670	10	.84
1088	20	4	A	680	10	.84
1088	20	3	A	690	10	.85
1092	30	3	A	700	10	.90
1089	20	4	A	710	10	.82
1092	20	4	A	730	10	.86
1089	20	4	A	740	10	.85
1090	20	3	A	750	10	.85
627	10	3	D	820	10	.90
676	10	4	D	820	10	.85
940	10	1	Other	820	10	.89
1093	20	3	A	820	10	.86
637	20	4	D	830	10	.82
828	20	3	B	830	10	.85
942	20	1	Other	840	20	.89
1091	20	3	A	830	10	.86
630	20	4	D	840	10	.83
960	20	1	Other	840	10	.85
996	20	2	Other	840	10	.90
1045	10	1	Other	840	10	.82
1091	20	2	A	840	10	.88
819	20	3	B	850	10	.85
1088	20	4	A	850	10	.84
627	20	3	D	860	10	.85
1088	20	3	A	860	10	.99
1089	20	3	A	870	10	.85

NUM "B"	GAP (A-B)	Class	Region	DEN "E"	GAP (D-E)	R_{min}
1089	20	3	A	880	10	.87
825	20	3	B	890	10	.84
1089	20	3	A	890	10	.85
825	20	3	B	900	10	.85
1089	20	3	A	900	10	.85
828	30	3	B	910	10	.83
1088	20	2	A	910	10	.86
837	30	2	B	920	10	.84
1088	20	2	A	920	10	.86
838	30	2	B	930	10	.87
1088	20	3	A	930	10	.85
820	10	2	B	940	10	.87
832	20	1	B	940	10	.87
837	30	2	B	950	10	.87
838	30	2	B	960	10	.84
838	30	2	B	970	10	.87
1091	20	3	A	980	10	.86
1091	20	2	A	990	10	.86
1091	20	3	B	1000	10	.86
819	10	3	B	1010	10	.81
1088	20	2	A	1010	10	.86
1088	20	2	A	1020	10	.86
1088	20	2	A	1030	10	.86
1088	20	2	A	1040	10	.86
1088	20	2	A	1050	10	.86
1088	20	2	A	1060	10	.86
705	20	4	C	1070	10	.84
1091	30	4	A	1070	10	.87
698	10	2	C	1080	10	.92
788	10	1	B*	1080	10	.93
791	20	1	B*	1080	10	.93
980	40	4	Other	1080	10	.91
1091	10	3	A	1080	10	.87
1088	20	3	A	1100	10	.82

*Short Wavelength Side

Selecting the best wavelength candidates for this four-wavelength model involves a trade-off of competing considerations such as the degree of accuracy that is necessary (e.g., for general population screening tests, a lower accuracy may be acceptable compared to a high level of accuracy needed for measuring and controlling the insulin dosage of a diabetic) and typical instrument

design parameters such as product cost (e.g., usability of low-cost IRED's as the light source instead of the high power requirement of a filament-type light bulb). In addition, the minimum risk of encountering an erroneous blood glucose reading is considered as well.

The data in Table III illustrates a number of different regions of the spectrum that provide prime candidate wavelengths for measuring glucose level in the blood. Specifically identified are: "Region A" which covers a spectrum range of approximately 1076 to 1086 nm; "Region B" which covers a spectrum range of approximately 809 to 823 nm; "Region C" which covers a spectrum range of approximately 693 to 701 nm; and "Region D" which covers a spectrum range of approximately 614 to 628 nm.

The above-identified wavelengths represent the midpoint wavelengths or the half-way point between the "A" and "B" wavelengths in Table III. In addition, Table III identifies other candidate mid-point wavelengths which are also practical. These wavelengths are identified as "other" and include: approximately 671 nm, approximately 782 nm, and approximately 1040 nm.

Further, the "class" column corresponds to the shape of the peak of the correlation versus wavelength curve as the "B" value in the numerator is varied. Figures 18A-D illustrate the classes of peaks which correspond to the shape of the correlation versus wavelength curve. Figure 18A illustrates that in "Class 1", the log 1/I values are essentially insensitive to small wavelength errors which represents the ideal situation. Figure 18B shows that the "Class 2" peak allows normal commercial tolerance on center wavelengths of optical filters (plus/minus 2 nanometers). Figure 18C shows that the "Class 3" peak could require tighter than normal commercial tolerances on the center wavelength of the optical filters. A tolerance of approximately +/- 1 nanometer would be

required in this class. This tighter tolerance would increase the cost of such optical filters by perhaps a factor of two to four. Figure 18D illustrates that in "Class 4", the measurement is hypersensitive to wavelength errors and would require the optical filter to provide a virtually correct wavelength. A small error would have a significant negative affect on measurement accuracy. The cost of providing such optical filters could be increased by a factor of ten over "Class 3" filters.

Denominator gaps described in Table III (i.e., D-E) are only representative values. As is customary in near-IR quantitative measurement, the denominator gaps can be increased substantially without undue impact on the total correlation coefficient. Thus, for convenience only, the denominator gaps of approximately ten nanometers have been shown in most cases.

In a preferred embodiment, the optimum wavelength candidates shown in Table III are A=771 nm, B=791 nm, D=1070 nm, and E=1080 nm. These wavelength candidates conform to the logical measurement regions defined above for Regions "J" and "K" which remove inaccuracies resulting from water absorption. Furthermore, these wavelengths provide for the highest correlation and allow use of lowest cost IREDs. In addition, these values have "Class 1" characteristics in that they are insensitive to small wavelength errors.

Table IV reproduced below presents the various candidates for the six-wavelength model. The test data was derived in a similar fashion to the test data in Tables I and II. As would be expected, there are a smaller number of candidates for the six-wavelength model compared to the four-wavelength model. This is a direct result of the fundamental difference between the two algorithms. The six-wavelength match uses second

derivatives of the optical curve. The second derivative is only of value at the peak absorption points, whereas the first derivative algorithms have twice as many possible candidates since measurement can be made on either side of the peak absorption point.

Table IV

d^2OD/d^2OD for All Denomination, (D-E: E-F - 10)

(R > .8)

Criteria: Must be OK on 3 People, "R_{min}" is minimum for lowest person

DEN "E"	R_{min}	"B"	GAP (A-B)& (B-C)	CLASS	DENOMINATOR GAP
650	.85	635	10	4	10
650	.88	691	20	4	10
650	.86	770	20	3	10
650	.90	791	10	3	10
650	.88	925	10	2	10
650	.84	1000	20	2	10
650	.86	1065	10	2	10
667	.91	1065	40	2	40
667	.90	791	30	2	30
687	.94	825	20	1	50
820	.92	667	40	2	10
824	.94	667	20	2	30
844	.94	667	30	1	10
883	.92	667	30	3	10
910	.87	667	30	4	10
920	.85	656	30	3	10
920	.87	667	40	3	10
930	.90	667	40	2	10
940	.88	667	40	3	10
950	.82	791	30	2	10
960	.90	667	40	3	10
970	.88	667	40	3	10
980	.88	667	40	3	10
980	.85	825	20	3	10
990	.85	667	30	3	10
1040	.87	667	30	3	10
1050	.83	667	30	3	10
1050	.91	825	20	4	10
1060	.88	667	30	4	10
1070	.82	667	30	3	10
1080	.83	788	20	2	10

According to another embodiment of the present invention, Figure 20 illustrates a Non-invasive Self Monitoring Glucose Meter (NISMGM) 70 which is designed to

measure blood glucose levels using near-IR transmission through the distal portion of the index finger. In this embodiment, the entire analytical instrument, including near-infrared point sources 71 and 72, transmitter, detector 75, amplifier 90, data processing circuitry 78, battery power source unit 89 and readout 80 is contained within a lightweight hand-held unit 70.

As illustrated in FIG. 20, the near-infrared point sources 71 and 72, separated by light baffle 86, are positioned so that near-infrared energy being emitted from the source will be directed through window 91 and onto the skin of the individual. The near-infrared point sources used in a preferred embodiment are IREDs. Further, optical filters 92 and 93 are between the IRED and the window 91 for filtering near-infrared radiation exiting each IRED and thereby allowing a narrow band of near-infrared radiation of predetermined wavelength to pass through.

In a preferred embodiment, the four-wavelength model can be used with the following multiple linear regression algorithm:

$$C = K_o + K_1 [\log 1/I_A - \log 1/I_B]/[\text{Log } 1/I_D - \text{Log } 1/I_E] + K_2T_S + K_3T_A$$

where K_o through K_3 are the calibration constants described above, A, B, C and D are specific wavelengths where the optical data is being measured, T_S is the local surface temperature of the finger in degrees centigrade divided by 100 and T_A is the temperature of the air within the instrument in degrees centigrade divided by 100. Calibration constants K_2 and K_3 are independent regression terms.

In the embodiment shown in Figure 20, any wavelength candidates may be chosen as described above which yield

accurate glucose measurement levels. In a preferred embodiment, the wavelength candidates can be approximately A=771 nm, B=791 nm, C=1070 nm and D=1080 nm. The above wavelengths can be obtained using standard 880 nm IREDs including narrow band pass filters producing wavelengths at 770/790 nm, and standard 950 nm IREDs used at the 1070/1080 nm wavelengths. Also, IREDs having center wavelengths at longer wavelengths than 950 nm could be used as well.

In actual use, it is very important that the fingertip not be exposed to ambient light. Further, it is desirable that the actual measurement be made near the rear of the finger-nail. Figure 20 illustrates a Finger Sizer means 82 to securely position the user's finger inside the instrument and to provide sufficient blockage of ambient light. Spring 87 pushes the Finger Sizer 82 against the bottom of the individual's finger thereby providing a secure fit. Linear potentiometer 88 is connected to Finger Sizer 82 and can measure an individual's finger thickness. In addition, an inflatable diaphragm or foam iris (illustrated at 79) can be used to secure the individual's finger and shield light as well.

Figure 20 further illustrates a measurement reading output device which is a large LCD display 80. Display 80 is advantageously constructed in a large size to facilitate reading by potential users who may have poor eyesight, one of the side effects of diabetes.

In a preferred embodiment, the NISMGM comprises means for displaying blood glucose level in two systems: the mg /dl for U.S. use and the mmol/L for Canadian use. Processor/controller 78 shown in Figure 20 can perform this function. A change between the two display modes would typically only be required for initial setup. Thus, a slide type switch (not shown) positioned in a

non-convenient place (e.g., in the battery compartment) could be used for this function.

Figure 20 shows input/output connector 84 which allows the NISMGM to be connected to a "host instrument" which can determine the calibration constants for the instrument and transfer them automatically to the NISMGM. The input/output connector 84 could also be attached to an external keypad to allow manual entry of calibration constants.

The operation of the NISMGM is described as follows. Prior to making a finger measurement, a front panel push button 85 is pressed which provides for optical standardization which could be the "optical standard" derived from the empty chamber. This measurement would include a "dark correction," which can be a measurement with all IREDs off so that a light leak would be detected and automatically corrected.

Figure 20 illustrates that when the finger is inserted into chamber 76, a built-in thermistor 77 measures the finger's temperature. The temperature measurement will be made at two times, approximately five seconds apart, the actual temperature term T_S being determined by using a logarithmic prediction equation as described in U.S. Patent No. 4,286,376. Care should be taken that the finger holder 79 fits securely enough around the finger so as to block out light, and yet loose enough that pulse beating does not interfere with the measurement.

A second thermistor 73 is positioned inside the instrument for measuring the ambient temperature. The ambient temperature measurement could be measured at any time prior to the instrument's actual use, but preferably at the same time the optical standard is measured. No logarithmic prediction is needed for the optical measurement. Also, timing control means 74 in control

circuitry 78 provides a battery protection feature which shuts off the instrument within approximately two minutes of th last measurement. No off button would be required.

In a further embodiment of the present invention, the NISMGM instrument comprises a memory unit 83 for storing a user's measurement data over a period of time. A built-in clock feature could also store the times at which the measurements were taken. The user would then be able to take the instrument to a doctor who could connect it to an output device, thereby dumping the information. This would allow the doctor to obtain information on the glucose level variability that occurred, for example, during the month.

According to another embodiment of the invention utilizing near-IR transmission analysis techniques, near-IR light energy at bandwidths centering on one or more wavelengths of interest is transmitted through a blood-containing portion of the body of a test subject. The near-IR energy emerges from the test subject, generally opposite from the near-IR source, and is detected by a detector. Following amplification of the detector-generated signal, the amplified output is processed into an output signal indicating the amount of glucose in the subject's blood.

Figure 21 illustrates a Non-invasive Self Monitoring Glucose Meter (NISMGM) 1 which is designed to measure blood glucose levels using near-IR transmission through the distal portion of a test subject's finger. The analytical instrument contains at least one near-infrared energy source for introducing near-infrared energy into the test subject's finger. In one embodiment of the present invention, the introducing means comprises up to six or more near-infrared point sources (near-IR IREDs). IREDs 171 and 172 are shown for illustrative purposes in

Figure 21. The analytical instrument also utilizes detector 175 for det cting near-infrared energy emerging from the test subject's body part. Detector 175 is electrically connected to data processing means 178 which, according to its programming, processes the signal produced by the detector 175 into a signal indicative of the quantity of glucose present in the blood of the test subject. Amplifier 190 amplifies the signal produced by the detector 175 before it is received into the processing means 178.

As illustrated in Figure 21, the IREDs 171 and 172, detector 175 and processing means 178 are contained within a lightweight hand-held housing unit 170. In a preferred embodiment, housing unit 170 is machined or molded from plastic.

Illustrative IREDs 171 and 172 are separated by light baffle 186 and are positioned so that the near-IR energy is directed through window 191, which may be light scattering, and onto the skin of the test subject. Optical filters, illustrated at 192 and 193, are positioned between each IRED and the window 191 for filtering the near-IR light, thereby optimizing the band of near-IR light striking the subject.

An important feature of the present invention is the cartridge means 195 which engages the housing unit. In a preferred embodiment, the cartridge means 195 is replaceable and is plugged into the analysis instrument 170 through receiving port 196 as illustrated in Figure 22. Cartridge 195 includes electronic memory storage devices 197A and 197B for storing data regarding an individual user and instrument software. By way of example, memory device 197A, such as a RAM, stores a series of glucose readings, the time and the date of all measurements made by the analysis instrument, the total number of measurements made using a particular battery,

as well as calibration constants (unique to the individual user) for use by data processor 178. In a preferred embodiment, the memory device 197B is an EPROM-type chip that contains the software for operating the analytical instrument 170, thus facilitating re-programming of instrument 170 by inserting an updated cartridge.

In certain embodiments, cartridge 195 also comprises a power source means, such as the illustrated battery 189, for supplying power to the near-infrared quantitative analysis instrument. Memory devices 197A and 197B and battery 189 are in electrical communication with the processing means 178 via interface 198.

An instrument for non-invasive measurement of blood glucose should provide accurate readings for any individual's glucose level which may be anywhere from about 40 mg/dl to as high as 500 mg/dl. In a typical glucose tolerance test used for calibration, changes in an individual's glucose level can be expected within the range of approximately 50 mg/dl to approximately 150 mg/dl. As a result, providing a custom calibration for an instrument covering the entire range is essentially impossible. Extrapolating information from this small calibration data using the single variable term algorithms shown above can cause errors when measuring glucose levels in the extreme regions of the entire range of possible glucose levels. These potential errors result from the non-linearity of extrapolation values as illustrated in Figures 24A and 24B.

To correct for nonlinear extrapolation, algorithms comprising multiple regression terms are used which enable accurate prediction of blood glucose measurement over a wide range. Such terms can be individual log 1/I terms or can be a multiple number of first or second derivative terms with or without a normalizing

denominator. Extrapolation is most reliable, however, using normalized division terms which are self-correcting for many types of measurement variability, as illustrated in Figures 24C and 24D. This self-correction occurs because the numerator and denominator normally are multiplied by the same error, thereby self-cancelling the error. Examples of these terms include normalized first and second derivative division terms. In one embodiment, algorithms containing two or more of the normalized division terms are used.

Data on a plurality of physical parameters of the test subject can also be utilized in conjunction with multiple wavelength near-infrared analysis, as in prior U.S. Patent No. 4,633,087, to improve the accuracy of the present blood glucose measurements. Further, blood glucose measurement accuracy can be improved by eliminating error which may result from bias shift in the near-infrared sources.

Each replaceable cartridge 195 is identified as belonging to a specific individual, because it contains custom calibration values for that individual. A user protection means is provided to insure that a replacement cartridge containing an individual's calibration information is used only by that individual, in the proper unit. In one embodiment, user protection is accomplished by a "handshake" code transmitted between the replacement cartridge and the unit. The encoding procedure comprises copying one or more calibration constant in the cartridge into the unit, which constant is used as the "handshake." In a preferred embodiment, all calibration constants for a particular individual are used as the "handshake."

In the embodiment shown in Figure 21, wavelengths for conducting the near-IR analysis are chosen so as to yield accurate glucose measurement levels. In one embodiment,

the wavelengths are approximately A=771 nm, B=791 nm, C=1070 nm and D=1080 nm. The 771 nm and 791 wavelengths can be obtained using standard 880 nm center wavelength IREDs in combination with narrow bandpass filters. IREDs having center wavelengths at longer wavelengths, such as the standard 950 nm IRED, are useful for producing 1070 nm and 1080 nm output when combined with appropriate optical filters. In a preferred embodiment, the wavelengths are approximately A=667 nm, B=687 nm, D=1059 nm and E=1079 nm.

It is very important that the test subject's fingertip not be exposed to ambient light. Further, it is desirable that the actual measurement be made near the rear of the finger-nail. Finger stop 181 illustrated in Figure 21 facilitates properly positioning the test subject's finger. Figure 21 also illustrates a finger retainer 182 to securely position the user's finger inside the instrument and to provide sufficient blockage of ambient light. Spring 187 pushes the finger retainer 182 against the bottom of the test subject's finger thereby providing a secure fit. Linear potentiometer 188 is connected to finger retainer 182 and can measure an individual's finger thickness. In addition, an inflatable diaphragm or rubber/foam iris (illustrated at 179) is used to secure the test subject's finger and shield light. The inflatable diaphragm can measure the blood pulse as well.

In a preferred embodiment, light shielding cover 194, shown in Figure 21, is rotatably attached to the analytical instrument 170 and closes over the finger chamber 176 providing essentially total blockage of ambient light. Cover 194 extends along the entire side of the analytical instrument and is securable at the base thereof in recess 183. Rubber strip 199 is secured to cover 194 and further facilitates blocking ambient light.

To facilitate the instrument's use by both adults and children, the finger measurement sections of the instrument allow for two or more different sizes of inserts. As illustrated in Figures 25A and 25B, insert 31A is suitable for the size of adult fingers and insert 31B is suitable for the size of children's fingers. Inserts accommodating a finger of any size can be used.

Figure 21 further illustrates an LCD display 180. Display 180 is advantageously constructed in a large size to facilitate reading by potential users who may have poor eyesight, one of the side effects of diabetes.

In a preferred embodiment, the analytical instrument comprises means for displaying blood glucose level in two systems: the mg/dl unit for U.S. use and the mmol/L unit for Canadian use. Processor means 178 shown in Figure 21 can perform this function. A change between the two display modes would typically be made during initial setup. Thus, a slide-type switch (not shown) positioned in a non-convenient place (e.g., in the battery compartment) could be used to select the desired display.

Figure 23 shows input/output connector 184 which forms part of the replaceable cartridge 195 and is electrically connected to controller/processor 178 of the analytical instrument 170. Input/output connector 184 allows the analytical instrument 170 to be connected to a "host instrument" which enables calibration constants determined by the host instrument, as described above, to be automatically transferred to the analytical instrument during calibration setup. In addition, the input/output connector 184 can be attached to an external keypad which allows manual entry of calibration constants.

The operation of the non-infrared quantitative analysis instrument will be readily apparent. Prior to making a finger measurement, a front panel push button 185 is pressed which provides for optical

standardization. Optical standardization is accomplished by measuring the empty finger chamber. Standardization also can include a "dark correction" measurement with all IREDs off so that a light leak is detected and automatically corrected for.

Figure 21 illustrates that when the finger is inserted into chamber 176, a built-in thermistor 177 measures the finger's temperature. The temperature measurement will be made at two times, approximately five seconds apart, with a temperature reading being determined by using a logarithmic prediction equation as described in U.S. Patent No. 4,286,376. Care should be taken to ensure that the finger holder 182 fits securely enough around the finger so as to block out light, and yet loosely enough to ensure that pulse beating does not interfere with the measurement. Better precision can be achieved if a single measurement involves inserting the finger twice.

A second thermistor 173 is positioned inside the analytical instrument 170 for measuring the ambient air temperature therein. The ambient air temperature measurement could be made at any time prior to the instrument's actual use, but preferably at the time the optical standard is measured. No logarithmic prediction is needed for the instrument air temperature measurement. Also, timing control means 174 in processor means 178 provides a battery protection feature which shuts off the instrument within a predetermined period of time after the a measurement is taken. In a preferred embodiment of the present invention, the battery protection feature shuts off the instrument within approximately two minutes of the last measurement. Although one may additionally be provided, this protection feature would alleviate the need for an "Off" button.

Processor means 178 and memory devices 197A and 197B advantageously enable a user to recall his or her previous glucose readings, including the time and date of those readings. In a preferred embodiment, between approximately eight and ten prior readings can be recalled in reverse order.

The analytical instrument preferably comprises means for indicating on display 180 the number of days remaining before the replaceable cartridge must be changed. This information can be accessed from memory device 197A at any time by pressing push button 185. In a preferred embodiment, this information will automatically appear on display 180 when the instrument is turned on, beginning five days prior to replacement. The analytical instrument 170 also includes a battery protection feature which prevents excessive battery use. During the calibration process, many battery-draining optical scans are required. In a preferred embodiment, pre-programmed circuitry permits a user to make no more than five successive readings without waiting a minimum of ten minutes before taking further readings.

In other versions, the analytical instrument utilizes a speech synthesizer 169 electrically connected to processor means 178 for providing instrument speech capability. This feature is used to provide patient prompting as well as providing an audio readout. This is of particular value to patients whose eyesight is excessively poor.

In another aspect of the present invention, a lightweight hand-held instrument uses the principle of light interactance to measure blood glucose level non-invasively by locating an optical transmitter and a detector on the skin surface near either an artery or vein.

In a lightweight, hand-held interactance analysis instrument 250 illustrated in Figure 26, included is one or more means for providing at least one point source of near-infrared energy of a predetermined bandwidth of interest which is positioned within a first chamber 260 of the instrument 250. The near-infrared point source means is positioned so that near-infrared energy being emitted from the point source means will be focused by lens 252 through window 254 and onto the skin of the test subject. The near-infrared point source means may comprise one or a plurality of infrared emitting diodes (IREDs). Two such IREDs 256 and 258 are illustrated in Figure 26. In other embodiments employing a plurality of IREDs, three, four or more IREDs may be utilized as the point source means.

An optical detector, illustrated schematically in Figure 26 and designated by reference numeral 268, is disposed within a lower end portion of second chamber 270. Inner wall 274 is positioned between detector 268 and illumination section 260, thereby providing an optically-isolated mask which prevents near infrared radiation from the point source means and/or lens 252 from impinging directly on detector 268. The near-infrared optical detector 268 generates an electrical signal when near-infrared radiation is detected thereby.

The optical detector 268 is connected to the input of an electrical signal amplifier 262 by suitable electrical conducting means 263. Amplifier 262 may be an inexpensive integrated circuit (IC) signal amplifier, and amplifies the signals generated when near-IR energy strikes detector 268. The output of amplifier 262 is fed to a controller/data processor and display driver 264 which provides a signal to readout device 266.

Interactance analysis instrument 250 further includes a replaceable cartridge means 280 which engages the

housing unit. In a preferred embodiment, the cartridge means 280 is plugged into the analysis instrument 250 through receiving port 272 as illustrated in Figure 27. Cartridge 280 is substantially identical to cartridge 195 discussed above and includes a battery power source 276, an electronic memory storage device 278A, such as a RAM, for storing date regarding an individual user and memory storage device 278B, such as an EPROM, for storing the instrument's software. In addition, cartridge 280 performs the same operational functions as disclosed with reference to cartridge 195. Memory devices 278A and 278B and battery 279 are in electrical communication with controller/data processor 264 via interface 279.

In use, the analysis instrument 250 is positioned so that its flat bottom surface rests on the skin directly above a prominent vein of the wrist of the test subject. Interactance instrument 250 is particularly useful for measuring the blood glucose level of small children whose fingers may be too small to achieve accurate results using the analysis instrument of Figure 21.

In another aspect of the present invention, a method for custom calibrating the near-infrared analysis instrument for the individual user is disclosed. In conventional near-infrared analysis, the calibration procedure requires a significant number of "samples" (i.e., a set of optical measurements) with known laboratory analysis of the parameter of interest (e.g., protein in wheat). The need for individual laboratory analyzed samples in conventional analysis results from the fact that each sample, and accordingly the parameter measurement, is totally independent of the previous sample. For example, when calibrating an instrument to measure protein in wheat, each wheat sample requires separate laboratory analysis.

However, in custom calibration for blood glucose, that *a priori* assumption is not true. It is known that if a diabetic eats food, a diabetic's blood glucose level will increase over the next fifteen minutes to a half an hour. This known characteristic of the direction of change in an individual's blood glucose level is an important factor for simplified custom calibration.

Figure 28 illustrates an easy and reliable method for custom calibration wherein a plurality of blood samples are obtained from an individual at predetermined time intervals, which do not need to be of equal duration, and for a predetermined period of time. Blood glucose levels are then obtained for each blood sample by any suitable reference method such as a Glucose Meter 2300G, manufactured by Yellow Springs Instrument Co. This information will serve as the laboratory data. The blood samples and blood glucose level measurements can be obtained using any other suitable means, such as a commercially available Biostator.

In a preferred embodiment, the blood glucose level measurements are obtained from a widely available Self-Monitoring Glucose Meter ("SMGM"). The technique employed in SMGM's involves using a lancet to draw blood from a finger-tip. A drop of blood is then placed on a chemically loaded plastic strip which is inserted into the instrument. The instrument measures and then digitally displays the blood glucose levels.

The predetermined time period in which the blood samples are taken is typically approximately once every 10-20 minutes and for approximately one-half hour to an hour and a half. The blood glucose level data is then entered into any suitable computation instrument, such as a computer, which can perform multiple regression analysis. In a preferred embodiment, the blood glucose

level data is entered into the near-infrared analysis instrument.

Also in a preferred embodiment, the predetermined time interval is selected so as to obtain actual blood glucose measurements at different levels while the individual's blood is being "spiked" (i.e., caloric ingestion). For example, a first blood glucose reading is taken after an overnight fast. Following this reading, the individual will either take and ingest a dextrose solution or eat a meal which will elevate the individual's blood glucose level. An additional finger poke measurement is then made after approximately fifteen minutes. This is repeated approximately every fifteen minutes for one hour. A total of four finger poke measurements are taken, in the preferred embodiment. The sample blood glucose level measurements could also be taken at predetermined time intervals which are not of equal duration, for example, after ten minutes, twenty-five minutes, forty-five minutes and after one hour and ten minutes. The predetermined time interval can be any time interval which will enable the individual's blood glucose level to be measured during at least a period where the individual's blood glucose level changes.

During the time period in which the blood samples are taken, near-infrared optical measurements are made and recorded using the non-invasive blood glucose instrument. These optical measurements should be made approximately once per minute. A total of approximately 60 sets of optical information will be recorded in the preferred embodiment.

The method of the present invention is utilized to calibrate a near-infrared analysis instrument not only for blood glucose levels, but for any known characteristic of the blood. For example, *a priori* knowledge of insulin level characteristics in the body is

known and the method of the present invention could be used to calibrate a near-infrared instrument for measurement of insulin levels.

The calibration regression analysis performed on the optical measurements will be described hereinafter. The calibration regression analysis of the present invention utilizes means for linearly interpolating the blood glucose level measurements made from the individual blood samples with the near-infrared optical measurements. Specifically, linear interpolation is used to assign laboratory values to the near-infrared optical measurements, between adjacent pair of the four finger poke glucose level measurements, which are taken at approximately fifteen minutes apart in the preferred embodiment. The linear interpolation is performed to provide glucose values for the specific times that the optical measurements are made, thus becoming the independent variable of the regression analysis. Thus, in the preferred embodiment, a set of four actual finger poke measurements will provide information for approximately 60 sets of the near-infrared optical measurements. The regression analysis is performed by a signal processor in any suitable method, such as disclosed above.

Since linear interpolation involves mathematically assigning expected values based on known values using an interpolation algorithm, the potential for error exists. In near-infrared analysis, it is known that the laboratory value assigned at any particular time by the interpolation process will potentially be in error from the actual blood glucose value at that moment. These errors typically result from the inaccuracy of the SMGM readings and from errors due to using interpolated values between the times of SMGM readings.

Although potential for error in the interpolated values exists, considerable experimentation in near-infrared technology has shown that such errors do not significantly affect calibration accuracy. The reason that accuracy is not significantly sacrificed is that the number of calibration samples, i.e., near-infrared optical measurements, is much larger than the number of regression terms in the regression algorithm. For example, the regression analysis performed in the present invention, as disclosed above, can use approximately three regression terms. Typically, acceptable accuracy occurs in near-infrared calibration where approximately ten samples are used for each regression term. In a preferred embodiment, approximately 60 samples are used and the total number of regression terms is approximately three or four. Thus, approximately fifteen samples per regression term are used. Moreover, this procedure can be repeated over several days which will enhance the statistical significance.

A near-infrared noninvasive blood glucose measurement instrument which can be custom calibrated employing the method of the present invention is illustrated schematically in Figure 21, as disclosed above.

In a preferred embodiment, the need to provide a data link to a host computer is eliminated by enabling the individual sample blood glucose level measurements to be entered into the analytical instrument through a keyboard on the instrument itself (not shown).

The method for custom calibrating a non-invasive blood glucose measurement instrument according to the present invention can also be used to calibrate analytical instruments which utilize near-infrared reflectance or interactance, such as disclosed above.

This novel method overcomes the inconveniences of the prior art methods by providing easy and reliable custom

calibration of non-invasive blood glucose measurement instruments which can readily be done on an at-home basis.

Additional embodiments of near-infrared non-invasive blood glucose measurement instruments which can be custom calibrated according to the method of the present invention will be described with reference to Figures 29 and 30.

The near-infrared analytical instruments 311 and 441, illustrated in Figures 29 and 30 respectively, operate substantially identically as disclosed with reference to Figure 21 above. The custom calibration procedure will be described in two alternate methods. First, as illustrated in Figure 29, a calibration system 330 is connected to the analytical instrument 311 and collects both optical data as measurements are taken and the time of each measurement. The calibration system 330 also allows the glucose values from the finger poke measurements to be hand-entered via keypad 332 on the calibration system 330 at approximately 15-minute intervals for up to 1.5 hours. When sufficient data has been received, such as after the above-described predetermined time intervals, the calibration system performs a multiple regression analysis, calculating the calibration constants for the linear regression algorithms. The calculated calibration constants are then transferred to the replaceable cartridges 320 plugged into the calibration system 330, or into a replaceable cartridge installed in the analytical instrument 311, and another inserted into the calibration system 330. In this approach, the calibration system 330 could be in a doctor's office and could also provide a printout device for the replaceable cartridges.

An alternate approach, illustrated in Figure 30, does not require a calibration system as discussed above. In

this approach, the replaceable cartridge contains EPROMs programmed to perform multiple regression analysis. The analytical instrument 441 has a key pad 442 having, typically, 11 keys (e.g. "0" through "9" plus an ENTER key) to allow the finger poke readings to be entered. In another embodiment, the finger poke readings are entered from an external keyboard or a replaceable cartridge. After the regression analysis is performed, the analytical instrument stores the calibration constants in the replaceable cartridge. At the same time, the analytical instrument erases the regression program allowing the EPROM to be used to store time/data and glucose values for a predetermined period of time, e.g., three months.

In another aspect of the invention, a method is disclosed for providing custom calibration which is valid over a range of skin temperatures. It is well established that temperature affects the energy absorption in near-infrared water band. Further, since the human body does not maintain constant temperatures at the extremities, i.e., fingers, calibration accuracy can be improved by including the effects of temperature variation.

The effect of temperature variations in blood glucose calibration has a direct applicable analogy in near-infrared (NIR) agricultural instruments. For example, if calibration for measurement of protein in wheat is performed with all wheat samples near room temperature, large errors would occur if that calibration is then used to predict the protein in wheat samples at significantly different temperatures.

This potential error is largely avoided by deliberately changing the temperature of samples during wheat calibrations. For example, some wheat samples are stored in a refrigerator and then immediately measured on

an NIR instrument. Other wheat samples are stored in freezers and then immediately measured on the NIR instrument. This approach has proven to b very successful for agricultural products, such as wheat, and has proven to provide accurate measurements at extreme temperatures.

An analogous approach provides accurate blood glucose calibration. Specifically, an individual's finger temperature is forced to have a range during the calibration process. Optical recordings are taken during the calibration at a range of skin temperatures.

Finger temperature variations can be induced using any conventional approach. For example, according to one technique of the present invention a small vessel is filled with water at room temperature. The individual to be tested then inserts the hand into a plastic bag leaving the top edge of the bag open. The bagged hand is then inserted into the water avoiding water contact with the skin. The hand is left in the water for at least one minute. Good heat transfer will result as the water pressure will force the air out of the plastic bag thereby snugly pressing the plastic against the hand. The hand is then removed and the near-infrared measurement is performed. The above-described steps are then repeated using water having a different temperature, i.e., approximately 100 to 120°F. Although any number of different temperature measurements could be used, the above approach allows the calibration to be performed with three different temperatures, including a measurement with no water immersion.

A test was performed to illustrate the effect of temperature variation on optical absorption wherein separate near-infrared measurements were taken for three finger temperature variations: (1) Hand in plastic bag immersed for 60 seconds in cool tap water (55°F); (2)

Normal skin temperature (no water immersion); and (3) Hand in plastic bag immersed for 60 seconds in warm water (103°F).

TABLE V

	Measured Finger Temperature	Peak Optical Absorption	Rate of Shift
Cool tap Water (55°F)	30.8°C	972.3 nm	
No Water Immersion	32.9°C	972.0 nm	$\frac{972.3 - 971.8}{30.8 - 34.3}$
Warm Tap Water (103°F)	34.3°C	971.8 nm	= -0.14 nm /°C

The test results set out in Table V above illustrate that the peak optical absorption shifts with finger temperature at a rate of approximately -0.14 nm/°C.

The rate of wavelength shift resulting from finger temperature variation is compared with the rate of wavelength shift caused by temperature variations in water. The magnitude of the wavelength shift can be calculated from the data in Figure 31.

Peak wavelength at 11°C = 980 nm

Peak wavelength at 96°C = 970 nm

Rate Of Shift = 980-970/1-96 = -0.11/°C

The test results indicate that the measured rate of shift is essentially identical for the finger measurement as it is for pure water. This illustrates that by imposing a temperature variation in the glucose calibration, the calibration will have greater validity over all finger temperatures.

Although the invention has been described in connection with certain preferred embodiments, it is not limited to them. Modifications within the scope of the following claims will be apparent to those skilled in the art. For example, accurate measurements can be obtained from parts of the body besides the wrist and the finger. The algorithm used to calculate blood constituent concentration(s) can be altered in accordance with known near-infrared analytical techniques.

Claims:

1. A near-infrared quantitative analysis instrument for non-invasive measurement of blood glucose in blood present in a body part of a subject, comprising:

(a) introducing means including a near infrared energy source for introducing near-infrared energy into blood present in a body part of a subject;

(b) detecting means for detecting near-infrared energy emerging from the body part;

(c) positioning means for positioning both the near-infrared introducing means and the detecting means closely adjacent to the body part; and

(d) processing means for processing a first electrical signal produced by the detector means into a second signal indicative of the quantity of glucose present in the blood of the subject.

2. The analysis instrument of claim 1 wherein said introducing means includes a filter means for selectively transmitting near-infrared energy, said filter means being disposed between said source and said body part.

3. The analysis instrument of claim 2 wherein said filter means selectively transmits near-infrared energy of between about 600 and 1100 nanometers.

4. The analysis instrument of claim 3 wherein said filter means selectively transmits near-infrared energy of between about 780 and 810 nanometers and between about 1070 and 1090 nanometers.

5. The analytical instrument of claim 3 wherein said filter means selectively transmits near-infrared energy of between about 770 and about 795 nanometers and between about 1065 and about 1085 nanometers.

6. The analysis instrument of claim 1 wherein said instrument is a lightweight hand-held unit.

7. The analysis instrument of claim 6 wherein said body part is a finger of said subject.

8. The analysis instrument of claim 6 comprising a housing means for preventing said body part from being exposed to ambient light.

9. The analysis instrument of claim 8 wherein said housing means comprises a sizer means for securely positioning said body part in said housing means.

10. The analysis instrument of claim 8 wherein said housing means further comprises an inflatable diaphragm for shielding exposure to ambient light.

11. The analysis instrument of claim 8 wherein said housing means comprises a first section and second section connected together by a pivot means whereby said first section and said second section pivot relative to one another about a pivot axis of said pivot means.

12. The analysis instrument of claim 6 comprising a display means for displaying blood glucose level.

13. The analysis instrument of claim 12 wherein said display means can display blood glucose level expressed in mg/dl and mmol/L.

14. The analysis instrument of claim 6 further comprising an input/output means electrically connected to said processing means for inputting and outputting data from and to an outside instrument.

15. The analysis unit of claim 6 further comprising a memory means for storing measurement data.

16. The analysis unit of claim 15 wherein said memory means includes a clock means for storing times at which said measurement data is stored in said memory means.

17. The analysis instrument of claim 1 wherein the processing means processes the first signal according to the formula

$$C = K_0 + K_1 [\log 1/I_A - \log 1/I_B] + K_2 T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$[\log 1/I_A - \log 1/I_B]$$

K_2 is a calibration constant, $\log 1/I_A$ and $\log 1/I_B$ each represent an optical density value at corresponding wavelengths A and B and T_S represents the local surface temperature of said body part.

18. The analysis instrument of claim 1 wherein the signal processing means processes the first signal according to the formula

$$C = K_0 + K_1 [\log 1/I_A - 2*\log 1/I_B + \log 1/I_C] + K_2T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is line slope of

$$[\log 1/I_A - 2*\log 1/I_B + 1/I_C]$$

K_2 is a calibration constant, $\log 1/I_A$, $\log 1/I_B$, and $\log 1/I_C$ each represent an optical density value at corresponding wavelengths A, B and C, and T_S represents the local surface temperature of said body part.

19. The analysis instrument of claim 1 wherein the signal processing means processes the signal according to the formula

$$C = K_0 + K_1 \frac{[\log 1/I_A - \log 1/I_B]}{[\log 1/I_D - \log 1/I_E]} + K_2T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$\frac{[\log 1/I_A - \log 1/I_B]}{[\log 1/I_D - \log 1/I_E]}$$

K_2 is a calibration constant, $\log 1/I_A$, $\log 1/I_B$, $\log 1/I_D$ and $\log 1/I_E$ each represent an optical density value at corresponding wavelengths A, B, D and E and T_S represents the local surface temperature of said body part.

20. The analysis instrument of claim 1 wherein the signal processing means processes the signal according to the formula

$$C = K_0 + K_1 \frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]} + K_2T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$\frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]}$$

K_2 is a calibration constant, log $1/I_A$, log $1/I_B$, log $1/I_C$, log $1/I_D$, log $1/I_E$, and log $1/I_F$ each represent an optical density value at corresponding wavelengths A, B, C, D, E and F, and T_S represents the local surface the temperature of said body part.

21. A non-invasive method for quantitatively analyzing blood glucose in blood of a subject, comprising:

(a) introducing at least one pair of wavelengths of near-infrared energy from a near-infrared energy source into blood within a body part of the subject, said pair of wave-lengths being within the range of about 600 to about 1100 nanometers;

(b) detecting near-infrared energy emerging from the subject with a detector which provides a signal upon detecting energy emerging from the subject; and

(c) processing the signal to provide a second signal indicative of the amount of glucose present in the body of the subject.

22. The method of claim 21 wherein said pair of wavelengths is centered on a wavelength within the range of about 600 to about 1100 nanometers.

23. The method of claim 21 wherein the first signal is processed according to the formula

$$C = K_0 + K_1 [\log 1/I_A - \log 1/I_B] + K_2T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$[\log 1/I_A - \log 1/I_B]$$

K_2 is a calibration constant, $\log 1/I_A$ and $\log 1/I_B$ each represent an optical density value at corresponding wavelengths A and B and T_S represents the local surface temperature of said body part.

24. The method of claim 21 wherein the first signal processing means processes the signal according to the formula

$$C = K_0 + K_1 [\log 1/I_A - 2*\log 1/I_B + \log 1/I_C] + K_2T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is line slope of

$$[\log 1/I_A - 2*\log 1/I_B + 1/I_C]$$

K_2 is a calibration constant, $\log 1/I_A$, $\log 1/I_B$, and $\log 1/I_C$ each represent an optical density value at corresponding wavelengths A, B and C, and T_S represents the local surface temperature of said body part.

25. The method of claim 21 wherein the signal processing means processes the signal according to the formula

$$C = K_0 + K1 \frac{[\log 1/I_A - \log 1/I_B]}{[\log 1/I_D - \log 1/I_E]} + K_2T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$\frac{[\log 1/I_A - \log 1/I_B]}{[\log 1/I_D - \log 1/I_E]}$$

K_2 is a calibration constant, $\log 1/I_A$, $\log 1/I_B$, $\log 1/I_D$ and $\log 1/I_E$ each represent an optical density value at corresponding wavelengths A, B, D and E and T_S represents the local surface temperature of said body part.

26. The method of claim 21 wherein the first signal processing means processes the signal according to the formula

$$C = K_0 + K_1 \frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]} + K_2T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$\frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]}$$

K_2 is a calibration constant, log $1/I_A$, log $1/I_B$, log $1/I_C$, log $1/I_D$, log $1/I_E$, and log $1/I_F$ each represent an optical density value at corresponding wavelengths A, B, C, D, E and F, and T_S represents the local surface temperature of said body part.

27. The analysis instrument of claim 1 wherein the first signal processing means processes the signal according to the formula

$$C = K_0 + K_1 \frac{[\log 1/I_A - \log 1/I_B]}{[\log 1/I_D - \log 1/I_E]} + K_2T_S + K_3T_A$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$\frac{[\log 1/I_A - \log 1/I_B]}{[\log 1/I_D - \log 1/I_E]}$$

K_2 and K_3 are calibration constants, log $1/I_A$, log $1/I_B$, log $1/I_D$ and log $1/I_E$ each represent an optical density value at corresponding wavelengths A, B, D and E, T_S represents the local surface temperature of said body part and T_A represents the ambient air temperature of said instrument.

28. The analysis instrument of claim 1 wherein the first signal processing means processes the signal according to the formula

$$C = K_0 + K_1 \frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]} + K_2T_S + K_3T_A$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$\frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]}$$

K_2 and K_3 are calibration constants, $\log 1/I_A$, $\log 1/I_B$, $\log 1/I_C$, $\log 1/I_D$, $\log 1/I_E$, and $\log 1/I_F$ each represent an optical density value at corresponding wavelengths A, B, C, D, E and F, T_S represents the local surface the temperature of said body part and T_A represents the ambient temperature of said instrument.

29. The method of claim 21 wherein the first signal processing means processes the signal according to the formula

$$C = K_0 + K_1 \frac{[\log 1/I_A - \log 1/I_B]}{[\log 1/I_D - \log 1/I_E]} + K_2T_S + K_3T_A$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$\frac{[\log 1/I_A - \log 1/I_B]}{[\log 1/I_D - \log 1/I_E]}$$

K_2 and K_3 are calibration constants, $\log 1/I_A$, $\log 1/I_B$, $\log 1/I_D$ and $\log 1/I_E$ each represent an optical density value at corresponding wavelengths A, B, D and E, T_S represents the local surface temperature of said body part and T_A represents the ambient temperature of said instrument.

30. The analysis instrument of any of claims 17-20, 27 or 28 wherein the corresponding wavelengths are between about 600 and about 1100 nanometers.

31. The analysis instrument of claim 30 wherein said corresponding wavelength A is between about 780 and about 810 nanometers and said corresponding wavelength B is between about 1070 and about 1090 nanometers.

32. The analysis instrument of claim 30 wherein said wavelength A is about 771 nanometers, said wavelength B is about 791 nanometers, said wavelength D is about 1070 nanometers, and said wavelength E is about 1080 nanometers.

33. The analysis instrument of claim 1 wherein said energy source comprises means for emitting near-infrared energy at a plurality of center wavelengths, said plurality of center wavelengths being separated by a constant wavelength, said introducing means further comprising control means for powering said energy source such that near-infrared energy at each said center wavelength is sequentially introduced into said body part.

34. The analysis instrument of claim 33 wherein said energy source comprises a plurality of infrared emitting diodes and wherein said control means sequentially powers each said plurality of infrared emitting diodes.

35. The analysis instrument of claim 33 further comprising means for identifying which two of said center wavelengths provide the a maximum difference when said subject is measured at a time of low glucose level and at a time of higher glucose level.

36. The analysis instrument of claim 33 wherein said constant wavelength is 10 nanometers.

37. The analysis instrument of claim 17 wherein said energy source comprises a plurality of near-infrared emitting diodes.

38. The analysis instrument of claim 37 wherein said plurality of near-infrared emitting diodes comprises six near-infrared emitting diodes.

39. The analysis instrument of claim 37 wherein optical filters corresponding to optimum wavelength values for A and B for a given subject are installed in said instrument.

40. The method of claim 21 wherein said at least one pair of wavelengths is individually selected for a subject by the following:

(a) sequentially introducing near-infrared energy into said body part of a subject at a plurality of

center wavelengths, said plurality of center wavelengths b ing separated by a constant wavelength;

(b) measuring a glucose level of said subject at a time of low glucose level and measuring a glucose of said subject level at a time of higher glucose level; and

(c) determining from the measuring step which center wavelengths provide the maximum difference and using the determined wavelengths in subsequent measurements for said subject.

41. A near-infrared quantitative analysis instrument for non-invasive measurement of blood present in a body part of a subject, comprising:

(a) introducing means including a near infrared energy source for introducing near-infrared energy into blood present in a body part of a subject;

(b) detecting means for detecting near-infrared energy emerging from the body part;

(c) positioning means for positioning both the near-infrared introducing means and the detecting means closely adjacent to the body part;

(d) processing means for processing a first electrical signal produced by the detector means into a second signal indicative of the quantity of glucose present in the blood of the subject;

(e) a housing means for housing said introducing means, said detecting means and said processing means; and

(f) a replaceable cartridge means engaging said housing means comprising a memory means for storing data comprising said second signal.

42. A near-infrared quantitative analysis instrument of claim 41 wherein said near-infrared energy source comprises an infrared emitting diode.

43. An analysis instrument of claim 41 wherein said introducing means comprises a filter means for selectively

transmitting near-infrared energy, said filter m ans being disposed between said source and said body part.

44. An analysis instrument of claim 43 comprising a first filter means for selectively transmitting near-infrared energy of between about 780 and 810 nanometers and a second filter means for selectively transmitting near infrared energy of between about 1070 and 1090 nanometers.

45. An analysis instrument of claim 41 wherein said memory means for storing data is electrically connected to said processing means which comprises a clock means for storing times at which measurement data is stored in said memory means.

46. An analysis instrument of claim 45 wherein said memory means further comprises programmable means for storing software for operating the analytical instrument.

47. An analysis instrument of claim 46 wherein said programmable means comprises an erasable programmable read only memory.

48. An analysis instrument of claim 41 wherein said cartridge means further comprises a power source means for providing power to said analysis instrument.

49. An analysis instrument of claim 41 further comprising an input/output connection means for enabling data to be input to said processing means and for outputting to an external source data from said processing means.

50. An analysis instrument of claim 49 wherein said cartridge means comprises said input/output connection means.

51. An analysis instrument of claim 41 wherein said housing means comprises a retainer means for securely positioning said body part in said housing means.

52. An analysis instrument of claim 41 wherein said housing means further comprises means for shielding the detector means from exposure to ambient light.

53. An analysis instrument of claim 52 wherein said means for shielding the detector means comprises a cover rotatably secured to said housing means.

54. An analysis instrument of claim 41 further comprising a display means for displaying blood glucose level.

55. An analysis instrument of claim 54 wherein said display means displays blood glucose levels in mg/dl and mmol/L units.

56. An analysis instrument of claim 41 wherein said housing means further comprises a first temperature sensing means electrically connected to said processor means for sensing a skin temperature of said body part and producing a first temperature signal representative thereof.

57. An analysis instrument of claim 41 wherein said housing means further comprises a second temperature sensing means electrically connected to said processor means for sensing ambient temperature inside said instrument and producing a second temperature signal representative thereof.

58. An analytical instrument of claim 41 further comprising protection means for requiring that said cartridge which is custom calibrated for an individual be used in a specific analytical instrument.

59. An analytical instrument of claim 58 wherein said protection means comprises storing at least one calibration constant in each said specific analytical instrument and said cartridge which must be matched before the analytical instrument will operate.

60. An analytical instrument of claim 41 further comprising speech synthesizer means for providing audio

operational instructions and audio output corresponding to said second signal.

61. An analytical instrument of claim 41 wherein said processor means further comprises means for automatically correcting for bias drift in said second signal.

62. A method for calibrating a near-infrared analysis instrument for the measurement of blood glucose, said method comprising:

(a) obtaining a plurality of blood samples from an individual each at a first predetermined time interval during a predetermined period of time and obtaining a blood glucose level measurement for each said blood sample;

(b) obtaining near-infrared optical absorption measurements through a body part of said individual at a second predetermined time interval and during said predetermined period of time, and recording said measurements; and

(c) performing calibration regression analysis utilizing means for linearly interpolating said blood sample glucose level measurements with said near-infrared optical absorption measurements to calibrate said near-infrared analysis instrument for said individual.

63. The method as set forth in claim 62 wherein said first predetermined time interval is between approximately 10 and approximately 20 minutes.

64. The method as set forth in claim 62 wherein said second predetermined time interval is between approximately one and approximately three minutes.

65. The method as set forth in claim 62 wherein said predetermined period of time is between approximately 45 and approximately 90 minutes.

66. The method as set forth in claim 65 wherein said predetermined period of time is approximately 60 minutes.

67. The method as set forth in claim 63 wherein said first predetermined time interval is approximately 15 minutes.

68. The method as set forth in claim 62 wherein said first predetermined time interval comprises time periods at least one of which has an unequal duration relative to at least one other of said time periods.

69. The method as set forth in claim 62 wherein approximately 40 to approximately 90 optical absorption measurements are made.

70. The method as set forth in claim 69 where a regression analysis algorithm used in said linear interpolation utilizes approximately three or four regression terms.

71. The method as set forth in claim 62 further comprising the following steps:

(a) placing said body part in a plurality of environments, each of said environments having a temperature different from each other of said environments, and producing a temperature change in said body part from a normal temperature of said body part; and

(b) obtaining at least one of said near-infrared optical absorption measurements through said body part after said temperature change has been produced in said body part.

72. A method for calibrating a near-infrared analysis instrument for the measurement of an unknown value of a known characteristic of blood, said method comprising:

(a) obtaining a plurality of blood samples from an individual each at a first predetermined time interval during a predetermined period of time and obtaining a value of said known characteristic for each blood sample;

(b) obtaining near-infrared optical absorption measurements through a body part of said individual at a second predetermined time interval and during said

predetermined period of time, and recording said measurements; and

(c) performing calibration regression analysis utilizing means for linearly interpolating each said value of said known characteristic for each said blood sample with said near-infrared optical absorption measurements to calibrate said near-infrared analysis instrument for said individual.

73. A near-infrared quantitative analysis instrument for non-invasive measurement of a blood analyte present in a body part of a subject, comprising:

(a) introducing means including a near infrared energy source for introducing near-infrared energy into blood present in a body part of a subject;

(b) detecting means for detecting near-infrared energy emerging from the body part;

(c) positioning means for positioning both the near-infrared introducing means and the detecting means closely adjacent to the body part; and

(d) processing means for processing a first electrical signal produced by the detector means into a second signal indicative of the quantity of said analyte present in the blood of the subject.

74. A near-infrared quantitative analysis instrument for non-invasive measurement of a blood analyte present in a body part of a subject, comprising:

(a) introducing means including a near infrared energy source for introducing near-infrared energy into blood present in a body part of a subject;

(b) detecting means for detecting near-infrared energy emerging from the body part;

(c) positioning means for positioning both the near-infrared introducing means and the detecting means closely adjacent to the body part;

(d) processing means for processing a first electrical signal produced by the detector means into a second signal indicative of the quantity said analyte present in the blood of the subject;

(e) a housing means for housing said introducing means, said detecting means and said processing means; and

(f) a replaceable cartridge means engaging said housing means comprising a memory means for storing data comprising said second signal.

AMENDED CLAIMS
[received by the International Bureau on 09 December 1991 (09.12.91); original claims 1, 17 - 20 amended; other claims unchanged (6 pages)]

1. A near-infrared quantitative analysis instrument for non-invasive measurement of blood glucose in blood present in a body part of a subject, comprising:

(a) introducing means, including a near infrared energy source, for selectively introducing near-infrared energy of between about 600 and 1100 nanometers into blood present in a body part of a subject;

(b) detecting means for detecting near-infrared energy emerging from the body part;

(c) positioning means for positioning both the near-infrared introducing means and the detecting means closely adjacent to the body part; and

(d) processing means for processing a first electrical signal produced by the detector means into a second signal indicative of the quantity of glucose present in the blood of the subject.

2. The analysis instrument of claim 1 wherein said introducing means includes a filter means for selectively transmitting near-infrared energy, said filter means being disposed between said source and said body part.

3. The analysis instrument of claim 2 wherein said filter means selectively transmits near-infrared energy of between about 600 and 1100 nanometers.

4. The analysis instrument of claim 3 wherein said filter means selectively transmits near-infrared energy of between about 780 and 810 nanometers and between about 1070 and 1090 nanometers.

5. The analytical instrument of claim 3 wherein said filter means selectively transmits near-infrared energy of between about 770 and about 795 nanometers and between about 1065 and about 1085 nanometers.

6. Th analysis instrument of claim 1 wherein said instrument is a lightweight hand-held unit.

7. The analysis instrument of claim 6 wherein said body part is a finger of said subject.

8. The analysis instrument of claim 6 comprising a housing means for preventing said body part from being exposed to ambient light.

9. The analysis instrument of claim 8 wherein said housing means comprises a sizer means for securely positioning said body part in said housing means.

10. The analysis instrument of claim 8 wherein said housing means further comprises an inflatable diaphragm for shielding exposure to ambient light.

11. The analysis instrument of claim 8 wherein said housing means comprises a first section and second section connected together by a pivot means whereby said first section and said second section pivot relative to one another about a pivot axis of said pivot means.

12. The analysis instrument of claim 6 comprising a display means for displaying blood glucose level.

13. The analysis instrument of claim 12 wherein said display means can display blood glucose level expressed in mg/dl and mmol/L.

14. The analysis instrument of claim 6 further comprising an input/output means electrically connected to said processing means for inputting and outputting data from and to an outside instrument.

15. The analysis unit of claim 6 further comprising a memory means for storing measurement data.

16. The analysis unit of claim 15 wherein said memory means includes a clock means for storing times at which said measurement data is stored in said memory means.

17. A near-infrared quantitative analysis instrument for non-invasive measurement of blood glucose in blood present in a body part of a subject, comprising:

(a) introducing means including a near infrared energy source for introducing near-infrared energy into blood present in a body part of a subject;

(b) detecting means for detecting near-infrared energy emerging from the body part;

(c) positioning means for positioning both the near-infrared introducing means and the detecting means closely adjacent to the body part; and

(d) processing means for processing a first electrical signal produced by the detector means into a second signal indicative of the quantity of glucose present in the blood of the subject wherein the processing means processes the first signal according to the formula

$$C = K_0 + K_1 [\log 1/I_A - \log 1/I_B] + K_2T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$[\log 1/I_A - \log 1/I_B]$$

K_2 is a calibration constant, $\log 1/I_A$ and $\log 1/I_B$ each represent an optical density value at corresponding wavelengths A and B and T_S represents the local surface temperature of said body part.

18. A near-infrared quantitative analysis instrument for non-invasive measurement of blood glucose in blood present in a body part of a subject, comprising:

(a) introducing means including a near infrared energy source for introducing near-infrared energy into blood present in a body part of a subject;

(b) detecting means for detecting near-infrared energy emerging from the body part;

(c) positioning means for positioning both the near-infrared introducing means and the detecting means closely adjacent to the body part; and

(d) processing means for processing a first electrical signal produced by the detector means into a second signal indicative of the quantity of glucose present

in the blood of the subject wherein the signal processing means processes th first signal according to the formula

$$C = K_0 + K_1 [\log 1/I_A - 2*\log 1/I_B + \log 1/I_C] + K_2T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is line slope of

$$[\log 1/I_A - 2*\log 1/I_B + 1/I_C]$$

K_2 is a calibration constant, $\log 1/I_A$, $\log 1/I_B$, and $\log 1/I_C$ each represent an optical density value at corresponding wavelengths A, B and C, and T_S represents the local surface temperature of said body part.

19. A near-infrared quantitative analysis instrument for non-invasive measurement of blood glucose in blood present in a body part of a subject, comprising:

(a) introducing means including a near infrared energy source for introducing near-infrared energy into blood present in a body part of a subject;

(b) detecting means for detecting near-infrared energy emerging from the body part;

(c) positioning means for positioning both the near-infrared introducing means and the detecting means closely adjacent to the body part; and

(d) processing means for processing a first electrical signal produced by the detector means into a second signal indicative of the quantity of glucose present in the blood of the subject wherein the signal processing means processes the signal according to the formula

$$C = K_0 + K_1 \frac{[\log 1/I_A - \log 1/I_B]}{[\log 1/I_D - \log 1/I_E]} + K_2T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$\frac{[\log 1/I_A - \log 1/I_B]}{[\log 1/I_D - \log 1/I_E]}$$

K_2 is a calibration constant, $\log 1/I_A$, $\log 1/I_B$, $\log 1/I_D$ and $\log 1/I_E$ each represent an optical density value at corresponding wavelengths A, B, D and E and T_S represents the local surface temperature of said body part.

20. A near-infrared quantitative analysis instrument for non-invasive measurement of blood glucose in blood present in a body part of a subject, comprising:

(a) introducing means including a near infrared energy source for introducing near-infrared energy into blood present in a body part of a subject;

(b) detecting means for detecting near-infrared energy emerging from the body part;

(c) positioning means for positioning both the near-infrared introducing means and the detecting means closely adjacent to the body part; and

(d) processing means for processing a first electrical signal produced by the detector means into a second signal indicative of the quantity of glucose present in the blood of the subject wherein the signal processing means processes the signal according to the formula

$$C = K_0 + K_1 \frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]} + K_2T_S$$

wherein C is concentration of glucose present in the blood, K_0 is an intercept constant, K_1 is the line slope of

$$\frac{[\log 1/I_A - 2*\log 1/I_B + \log 1/I_C]}{[\log 1/I_D - 2*\log 1/I_E + \log 1/I_F]}$$

K_2 is a calibration constant, $\log 1/I_A$, $\log 1/I_B$, $\log 1/I_C$, $\log 1/I_D$, $\log 1/I_E$, and $\log 1/I_F$ each represent an optical density value at corresponding wavelengths A, B, C, D, E and F, and T_S represents the local surface the temperature of said body part.

21. A non-invasive method for quantitatively analyzing blood glucose in blood of a subject, comprising:

(a) introducing at least one pair of wavelengths of near-infrared energy from a near-infrared energy source into blood within a body part of the subject, said pair of wave-lengths being within the range of about 600 to about 1100 nanometers;

(b) detecting near-infrar d energy emerging from the subject with a detector which provides a signal upon detecting energy emerging from the subject; and

(c) processing the signal to provide a second signal indicative of the amount of glucose present in the body of the subject.

22. The method of claim 21 wherein said pair of wavelengths is centered on a wavelength within the range of about 600 to about 1100 nanometers.

23. The method of claim 21 wherein the first signal is processed according to the formula

STATEMENT UNDER ARTICLE 19

1	Replaces former claim 1 and adds the limitation that the near-infrared energy falls between 600 - 1100 nanometers.
2-16	Unchanged.
17	Corresponds to original claim 17 re-written in independent form.
18	Corresponds to original claim 18 re-written in independent form.
19	Corresponds to original claim 19 re-written in independent form.
20	Corresponds to original claim 20 re-written in independent form.

by removing a sample of blood (e.g. 5-10 ml) and performing one or more standard chemical tests. These types of tests are moderately expensive, require one class of trained technicians to remove the blood and another class of trained technicians to perform the chemical tests. Moreover, the results of the blood tests

FIG. 1

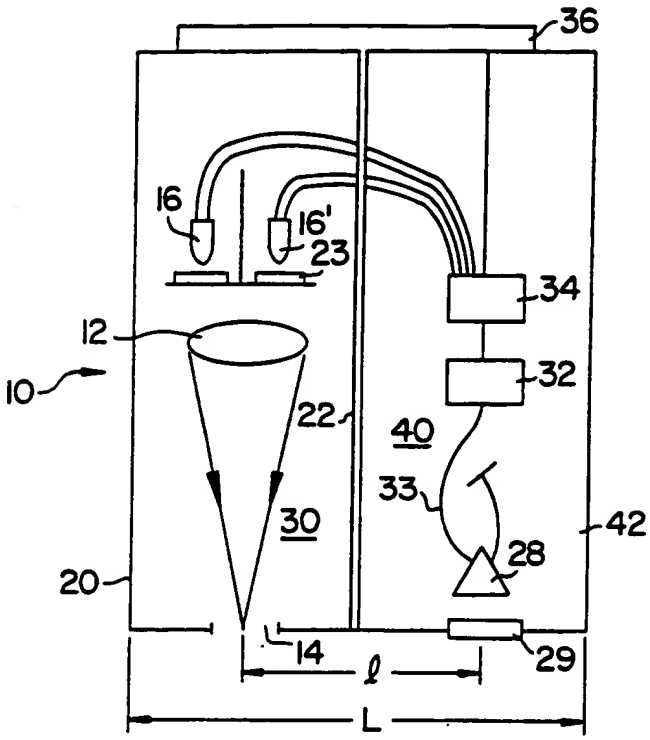

36
16
16'
23
34
12
10
32
22
40
33
42
30
28
20
14
29
ℓ
L

FIG. 3

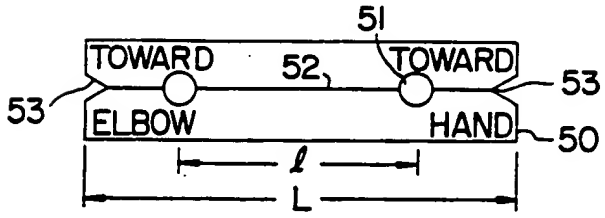

51
TOWARD
52
TOWARD
53
53
ELBOW
HAND
50
ℓ
L

FIG. 2A

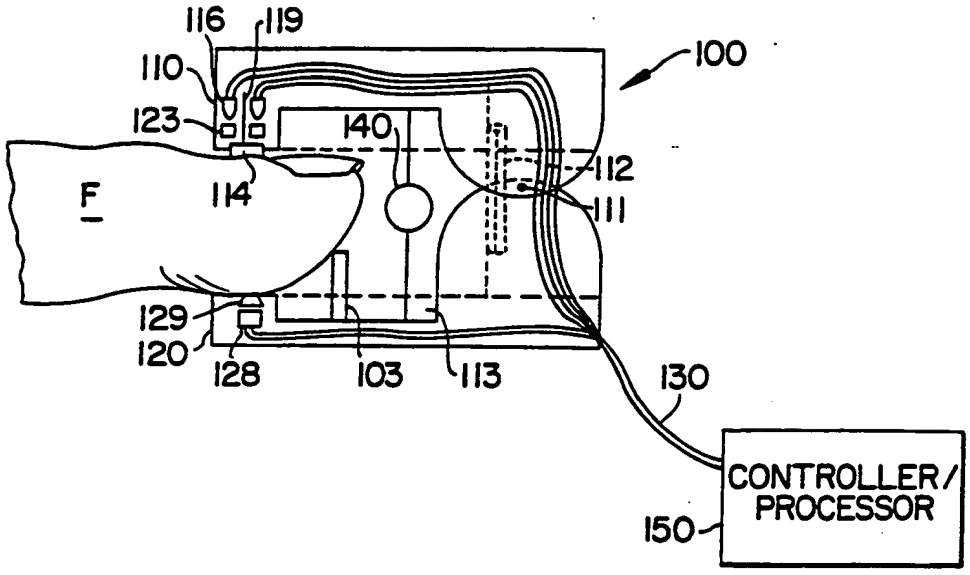
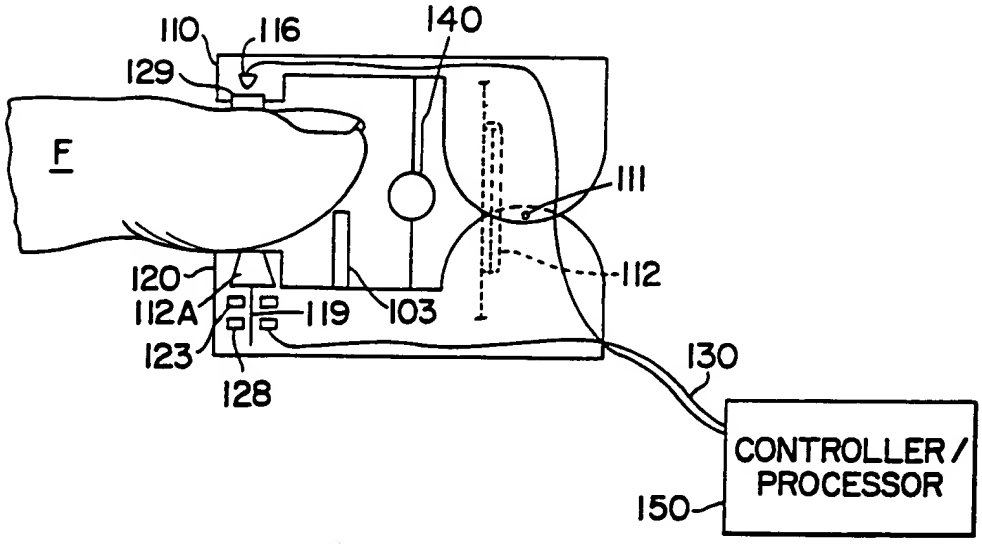

116
119
110
100
123
140
112
F
114
111
129
120
128
103
113
130
CONTROLLER/
PROCESSOR
150

FIG. 2B


110
116
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120
112
112A
119
103
123
130
128
CONTROLLER/
PROCESSOR
150

FIG. 4

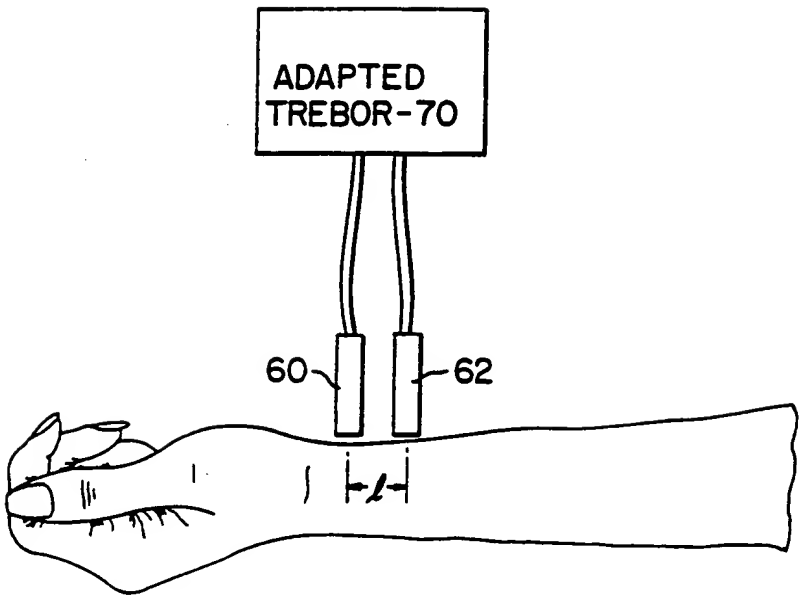


FIG. 5A

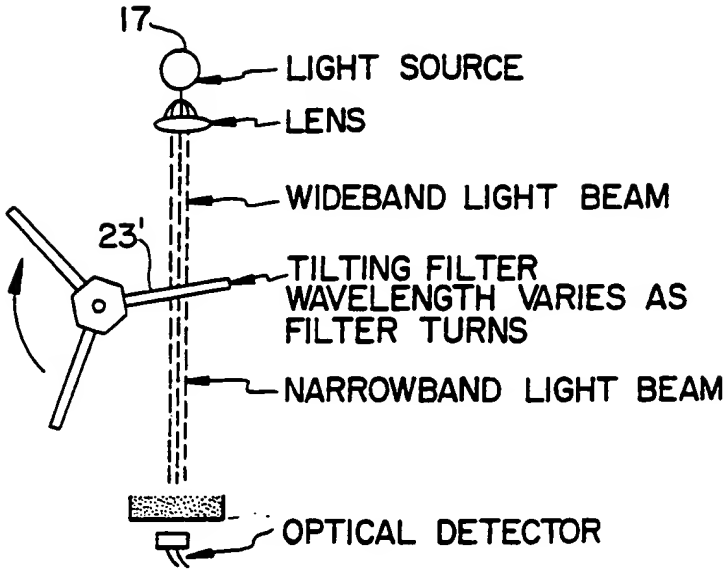

17
LIGHT SOURCE
LENS
WIDEBAND LIGHT BEAM
23'
TILTING FILTER
WAVELENGTH VARIES AS
FILTER TURNS
NARROWBAND LIGHT BEAM
OPTICAL DETECTOR

FIG. 5B

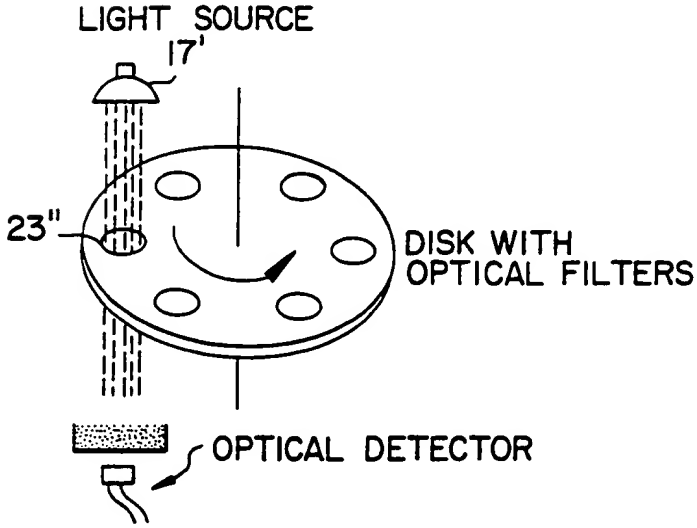

LIGHT SOURCE
17'
23"
DISK WITH
OPTICAL FILTERS
OPTICAL DETECTOR

FIG. 6

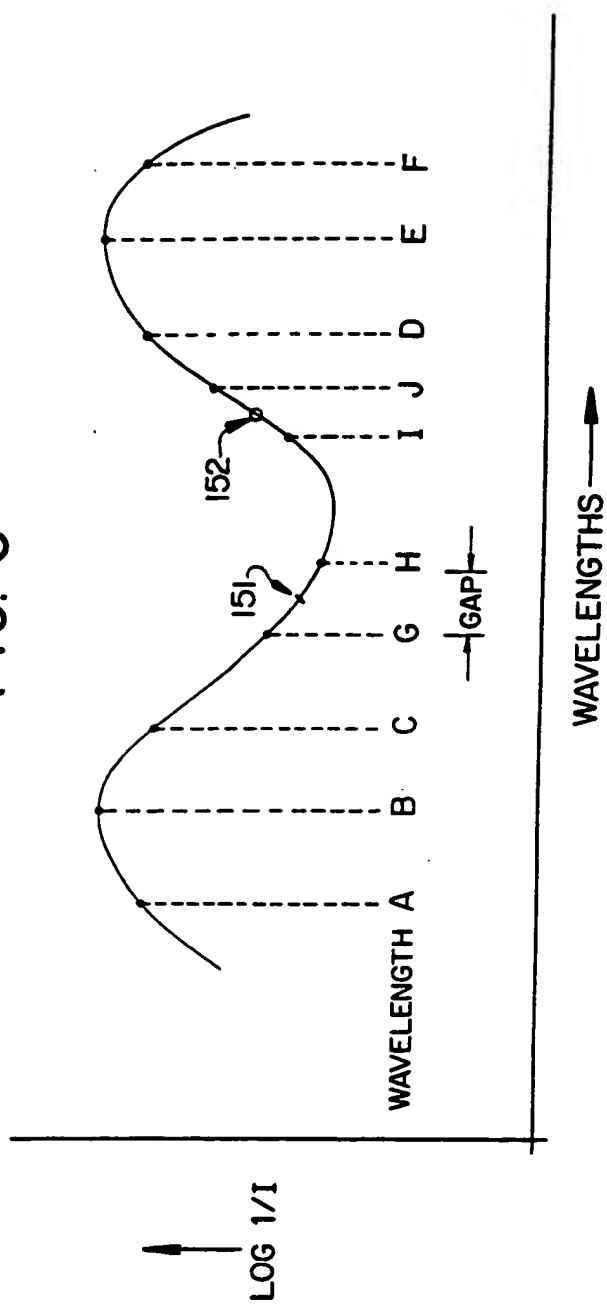
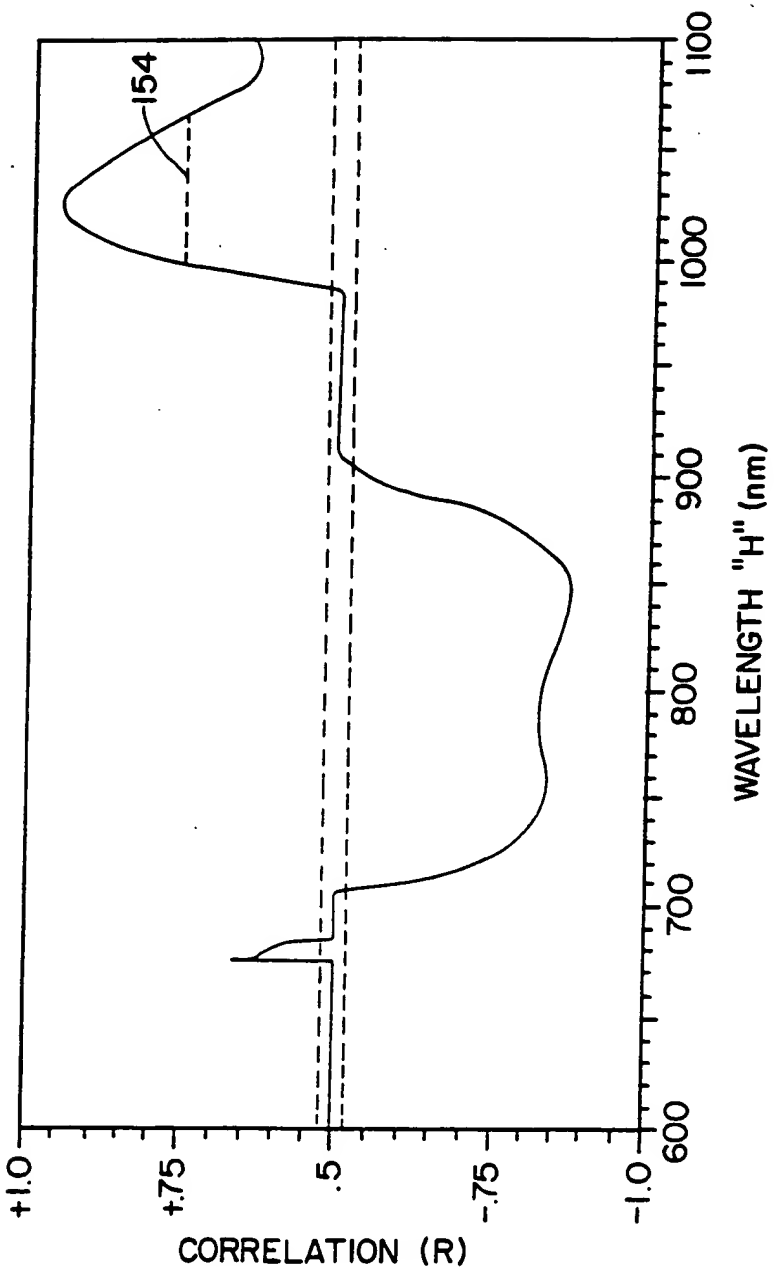


FIG. 7


154
1100
1000
900
800
700
600
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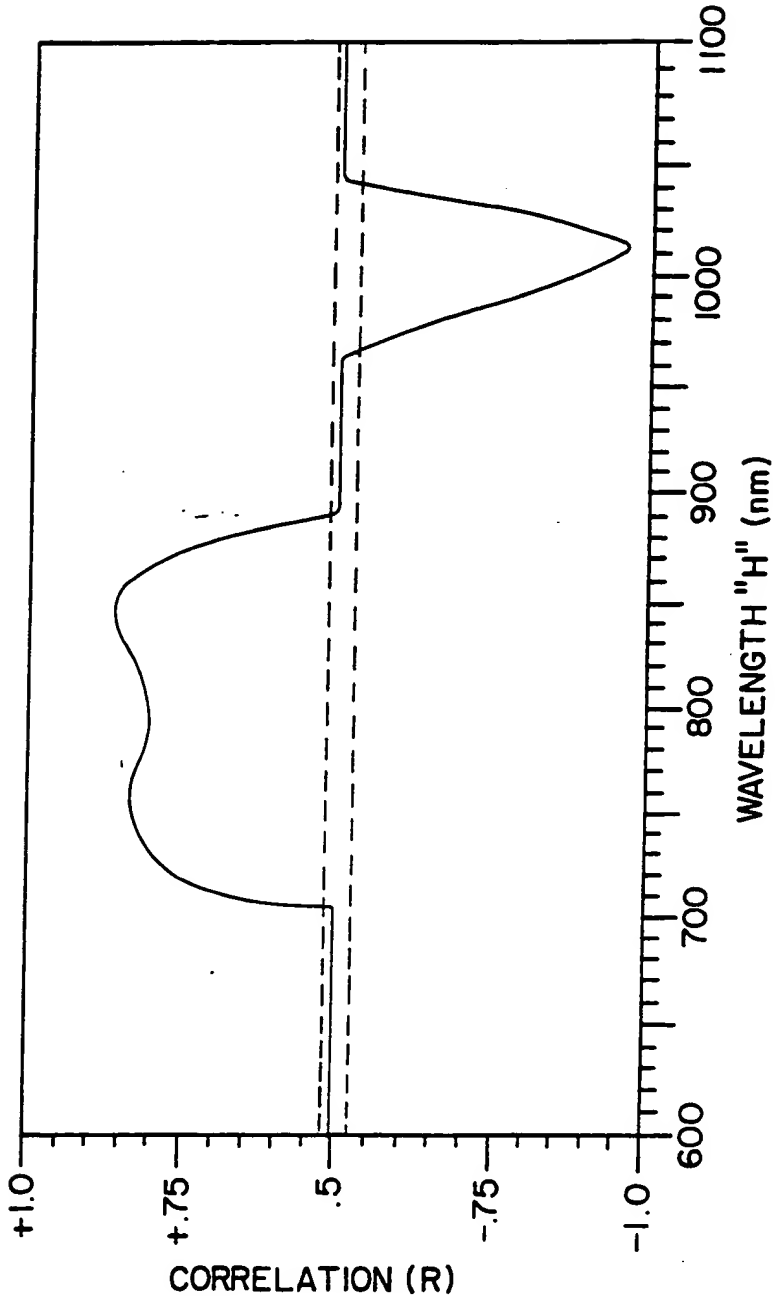
+1.0
+.75
.5
-.75
-1.0
CORRELATION (R)

FIG. 8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1000
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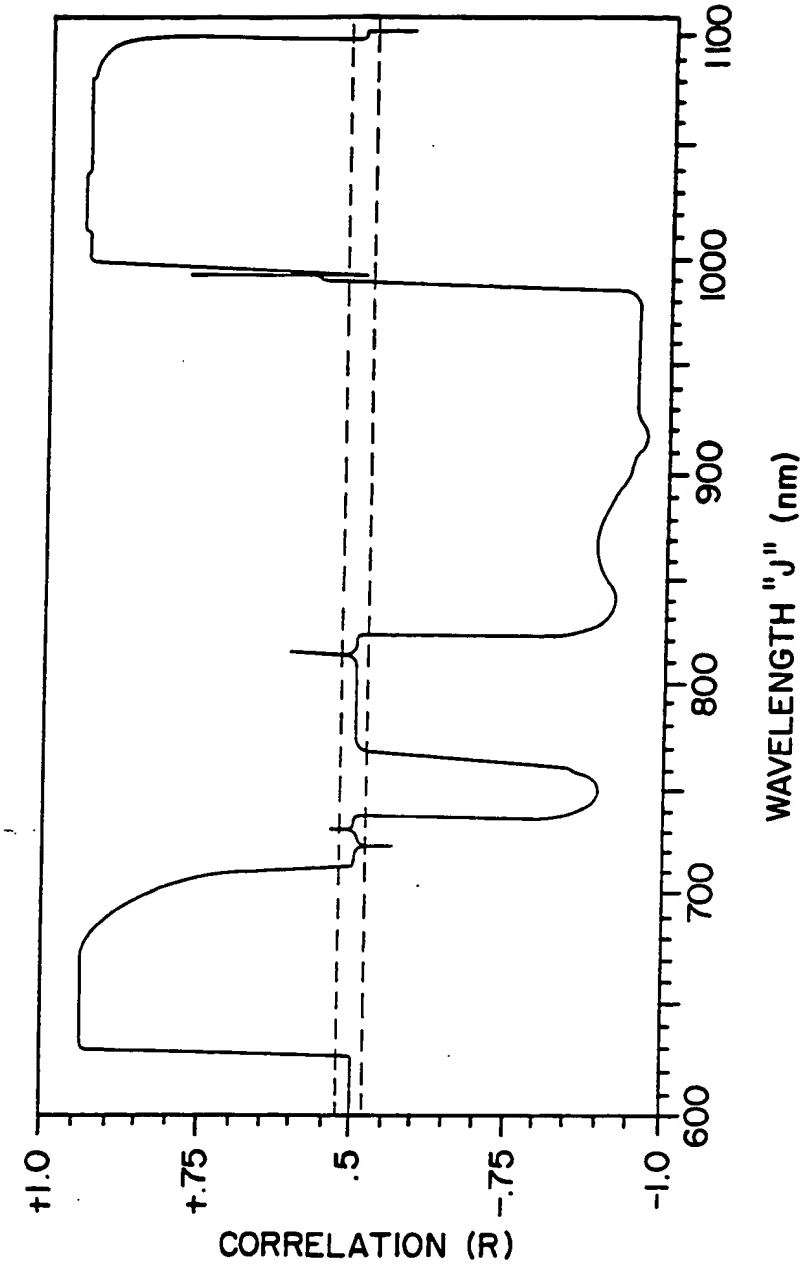
800
700
600
WAVELENGTH "H" (nm)
+1.0
+.75
.5
-.75
-1.0
CORRELATION (R)

FIG. 9


1100
1000
900
800
700
600
WAVELENGTH "J" (nm)
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+.75
.5
-.75
-1.0
CORRELATION (R)

FIG. 10

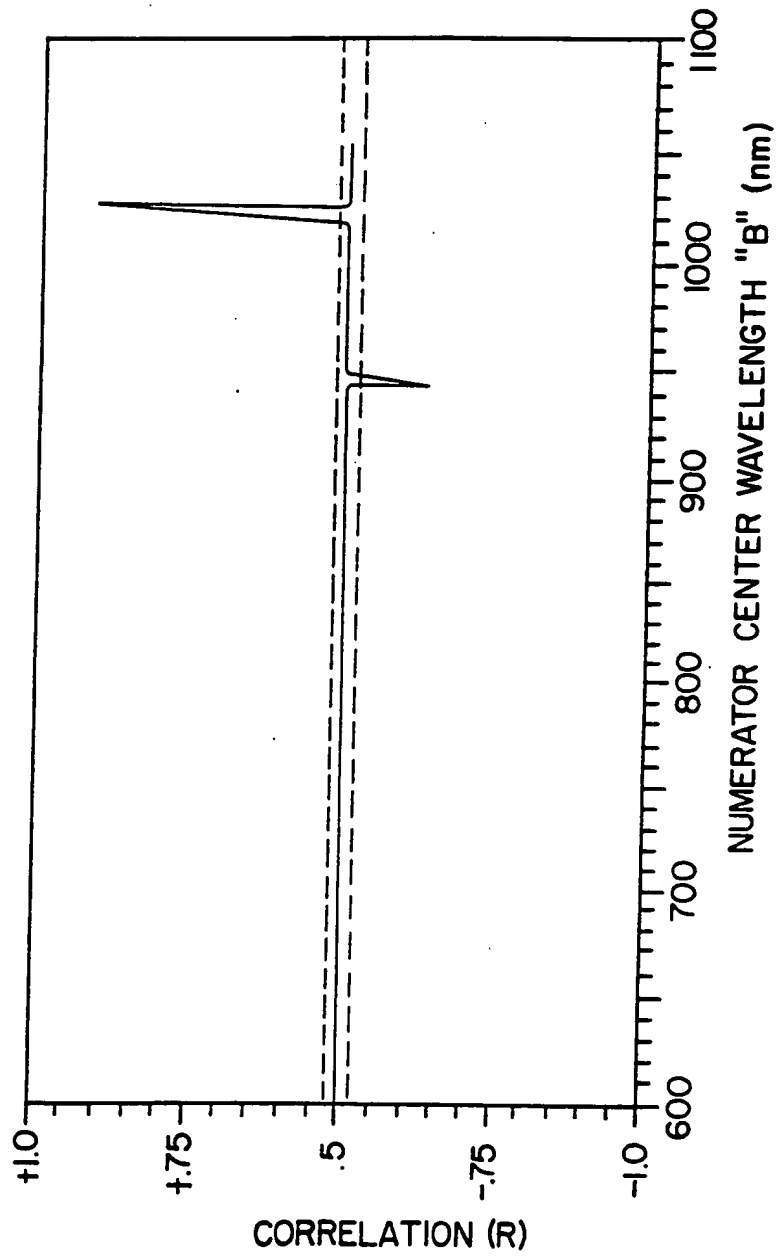
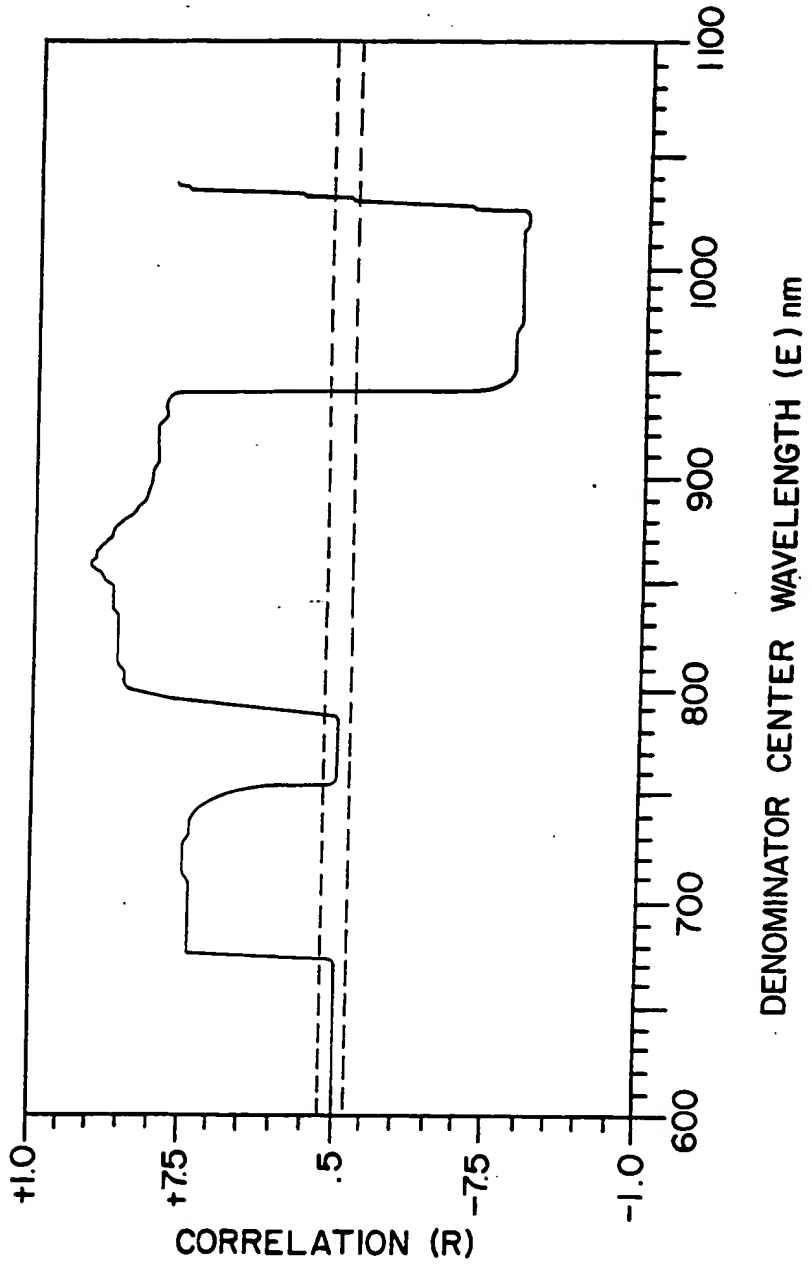

NUMERATOR CENTER WAVELENGTH "B" (nm)
1100
1000
900
800
700
600
+1.0
+.75
.5
-.75
-1.0
CORRELATION (R)

FIG. 11


+1.0
+.75
.5
-.75
-1.0
CORRELATION (R)
600
700
800
900
1000
1100
DENOMINATOR CENTER WAVELENGTH (E) nm

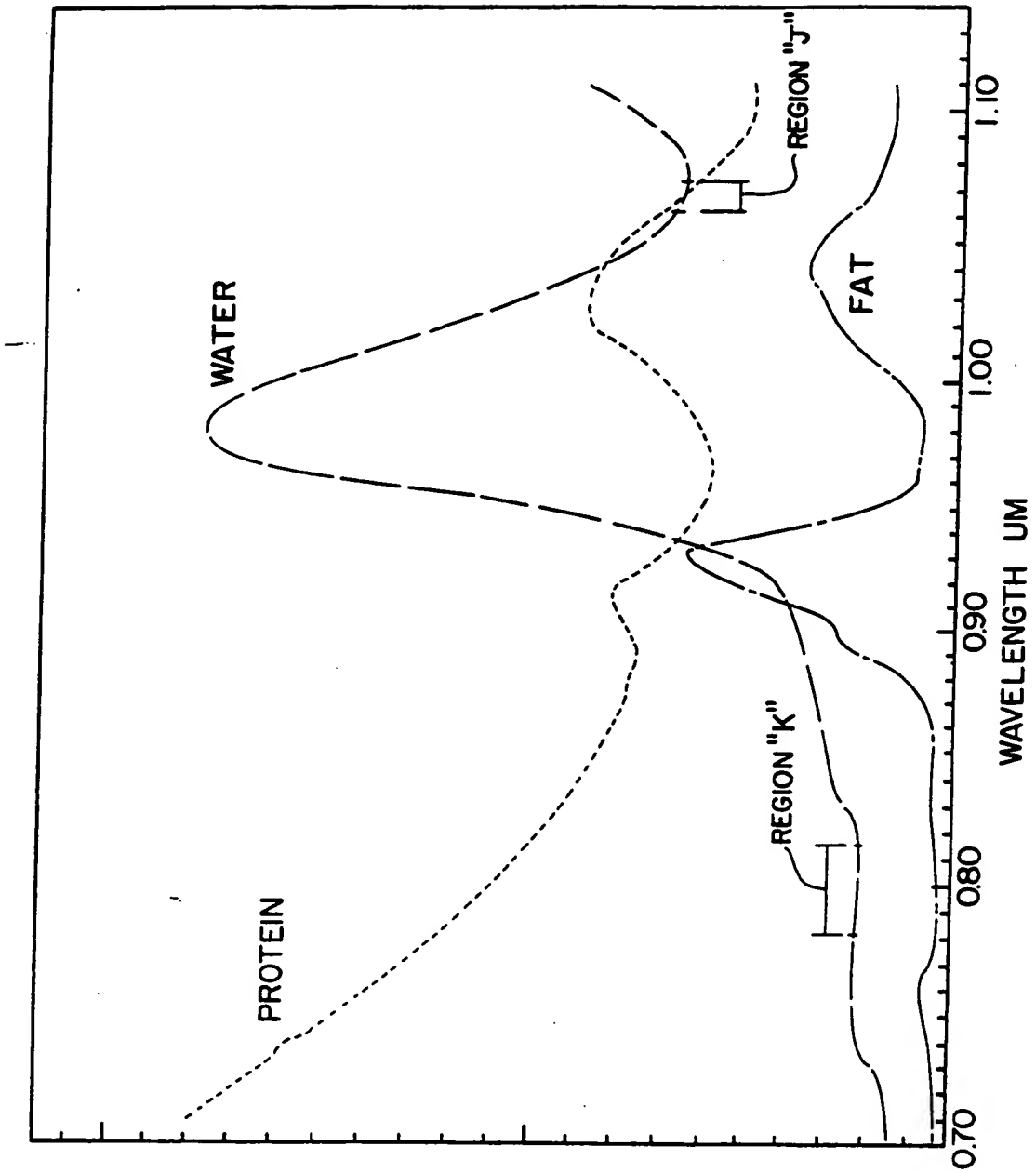

WATER
FAT
PROTEIN
REGION "J"
REGION "K"
0.70
0.80
0.90
1.00
1.10
WAVELENGTH UM

FIG. 12

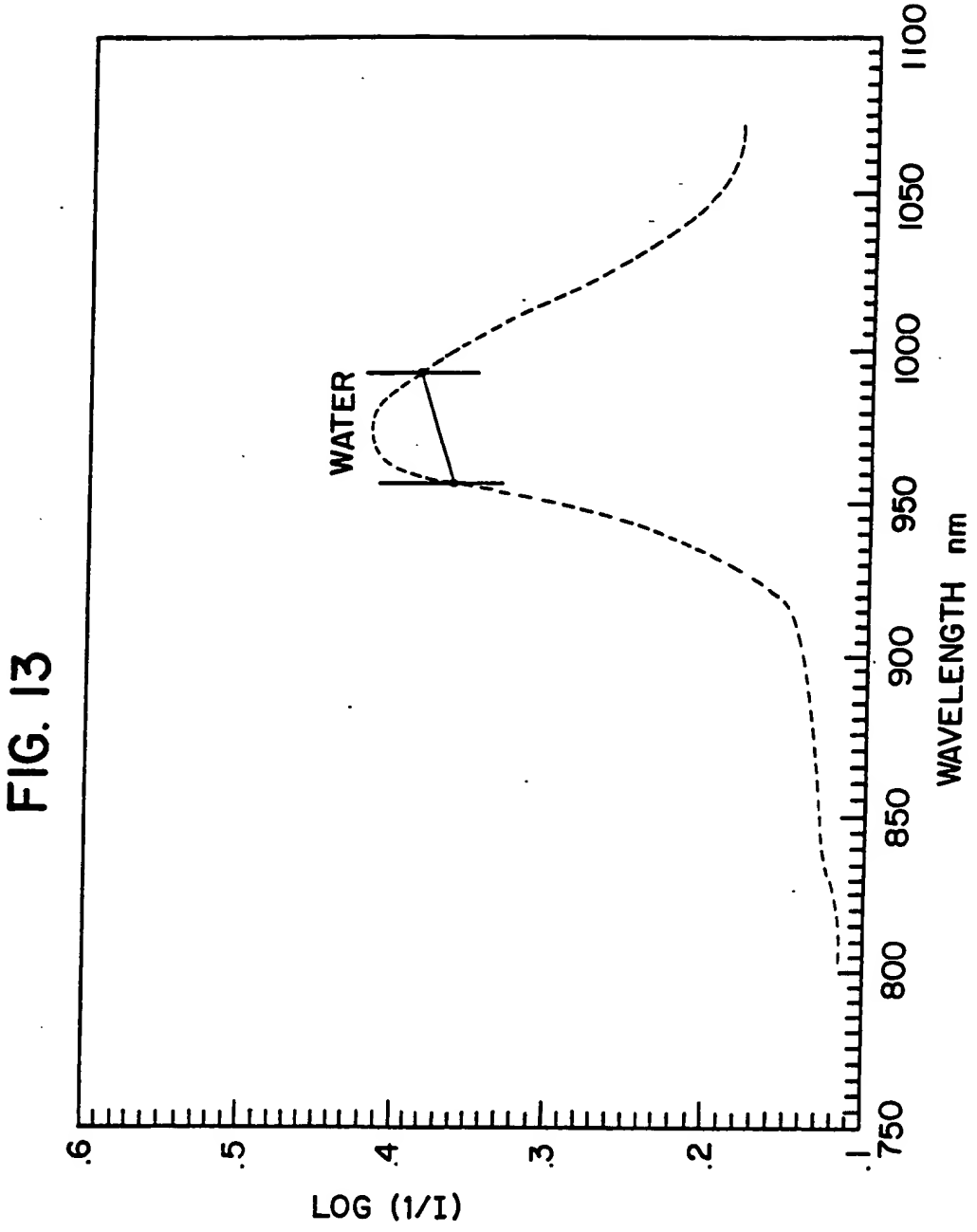
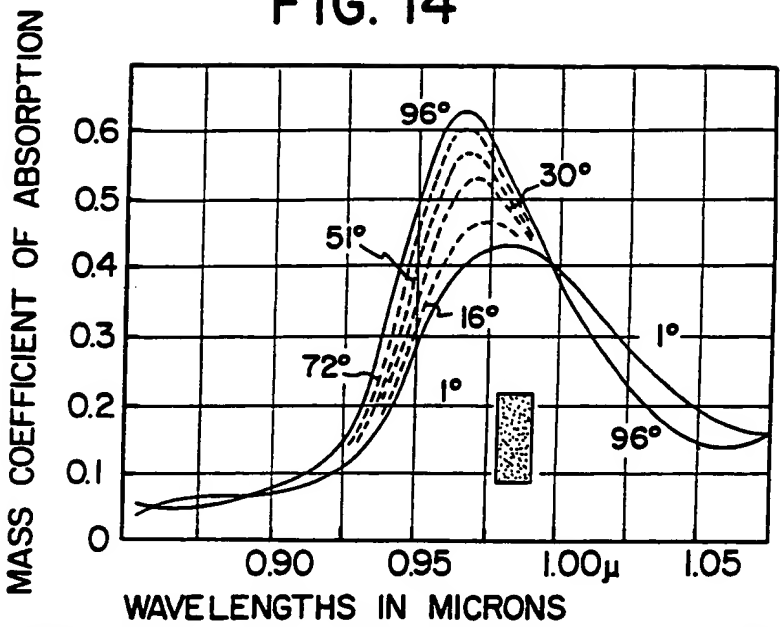

WATER
1100
1050
1000
950
900
850
800
750
WAVELENGTH nm
.6
.5
.4
.3
.2
.1
LOG (1/I)

FIG. 13

FIG. 14



ABSORPTION BAND (0.9-1.05μ) OF LIQUID WATER AT 0.5° TO 90°C.

FIG. 15

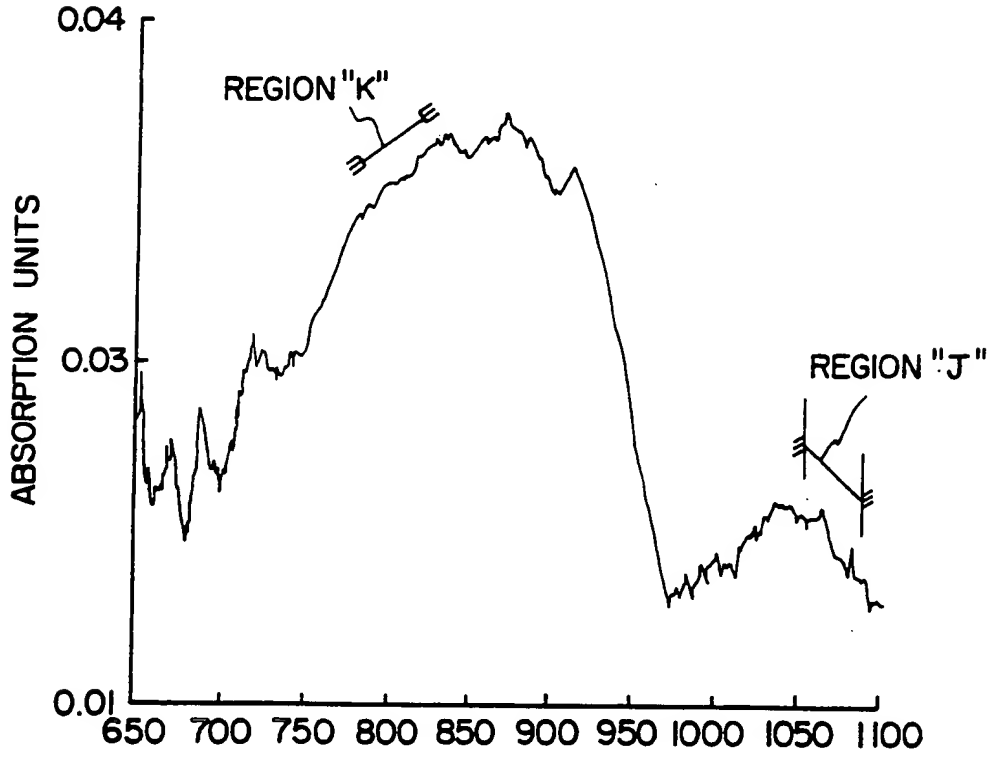


FIG. 16

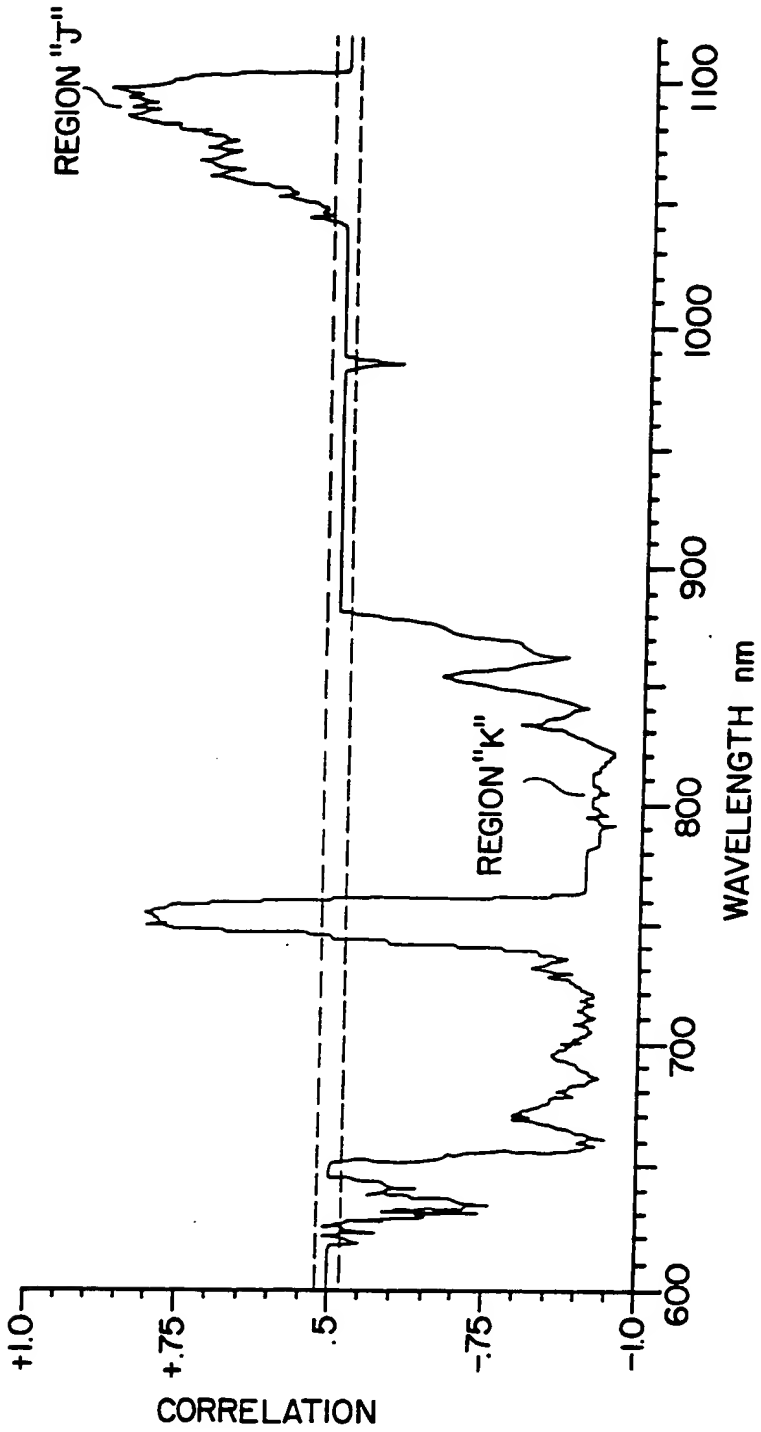

REGION "J"
REGION "K"
+1.0
+.75
.5
-.75
-1.0
CORRELATION
600
700
800
900
1000
1100
WAVELENGTH nm

FIG. 17

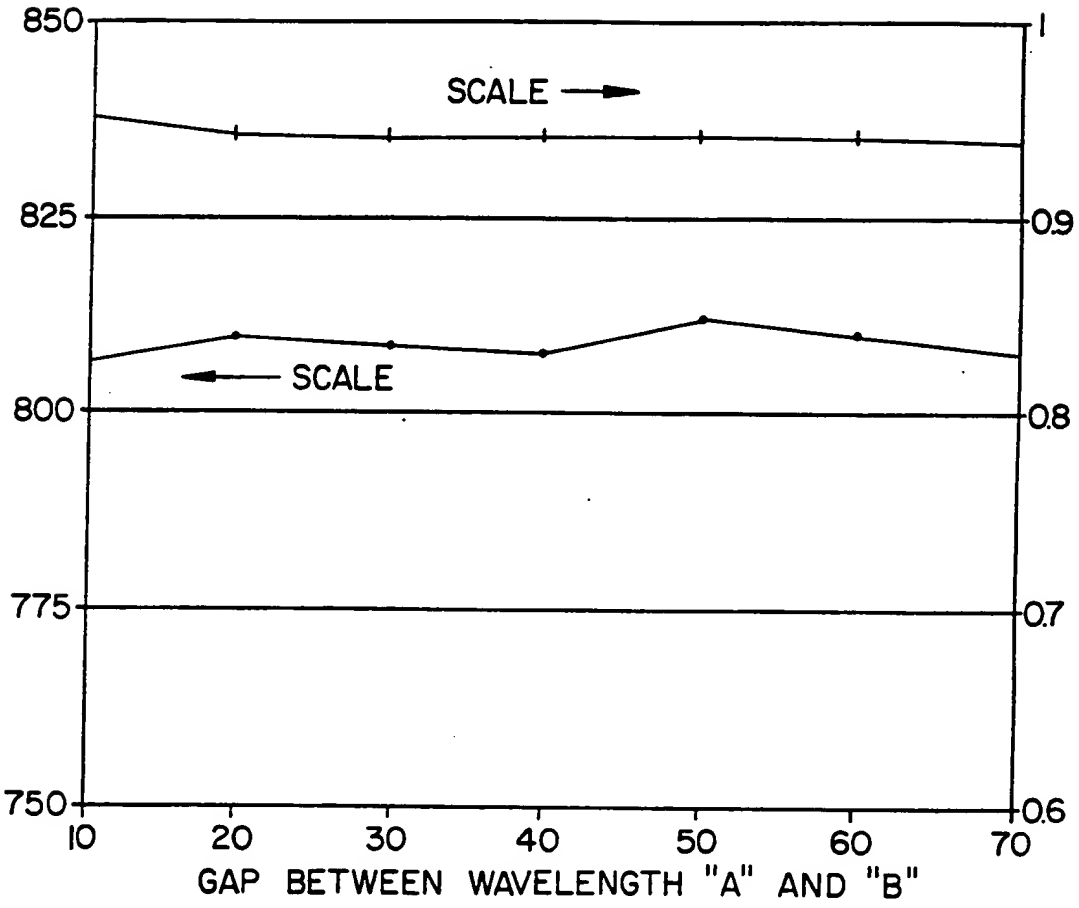

850
825
800
775
750
1
0.9
0.8
0.7
0.6
SCALE
SCALE
10
20
30
40
50
60
70
GAP BETWEEN WAVELENGTH "A" AND "B"

FIG. 18B

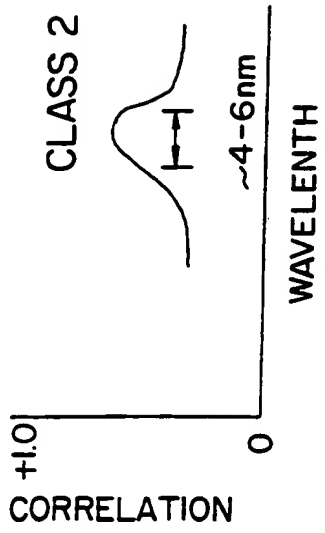


FIG. 18D

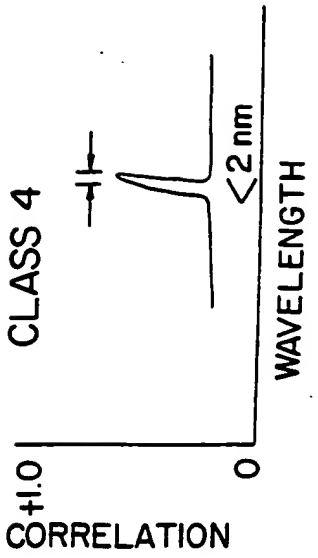


FIG. 18A

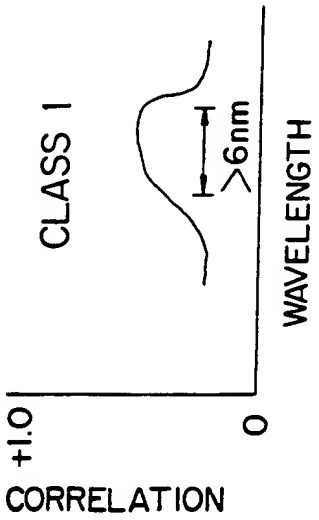


FIG. 18C

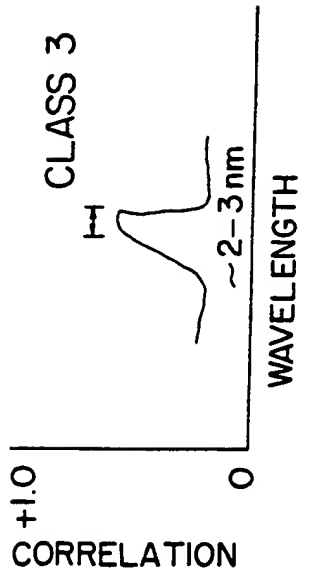


FIG. 19

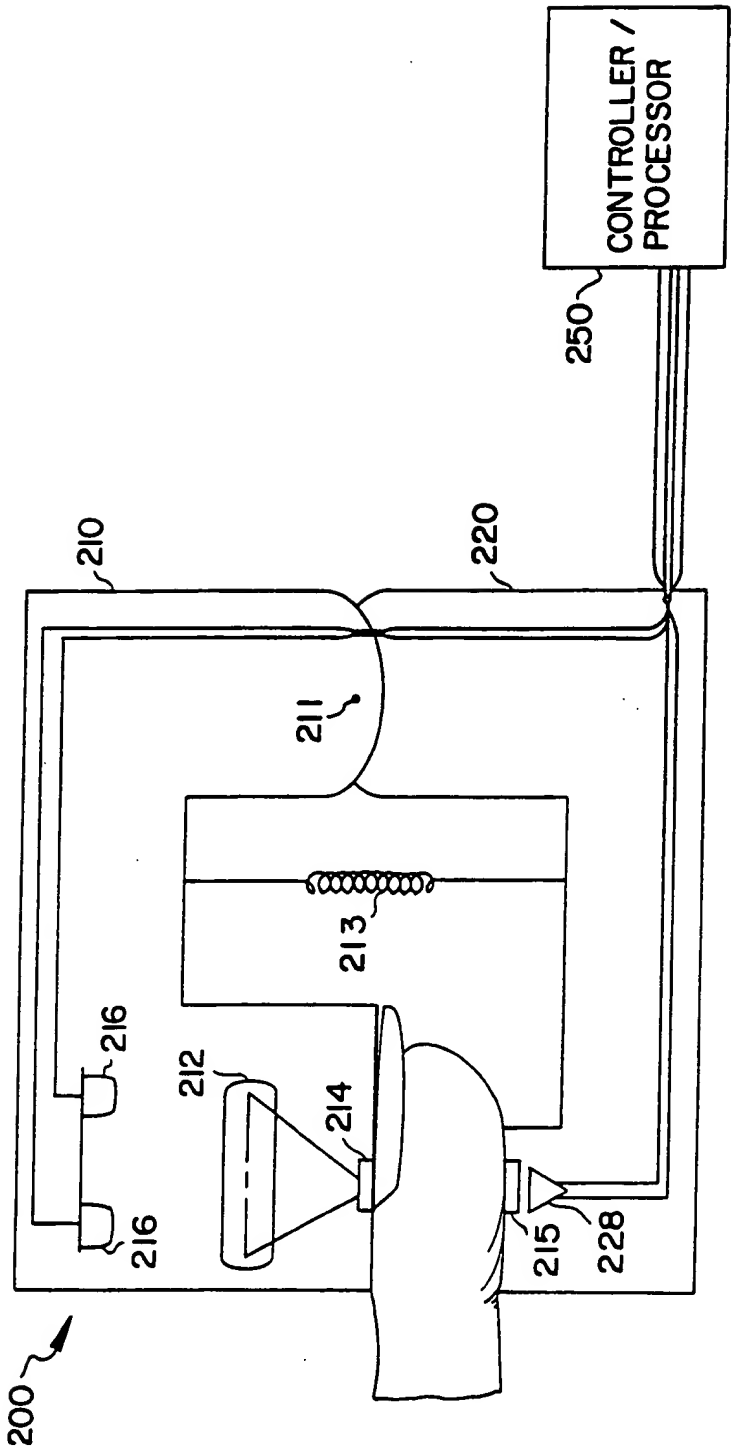

CONTROLLER / PROCESSOR
250
210
220
211
213
216
212
214
216
215
228
200

FIG. 20

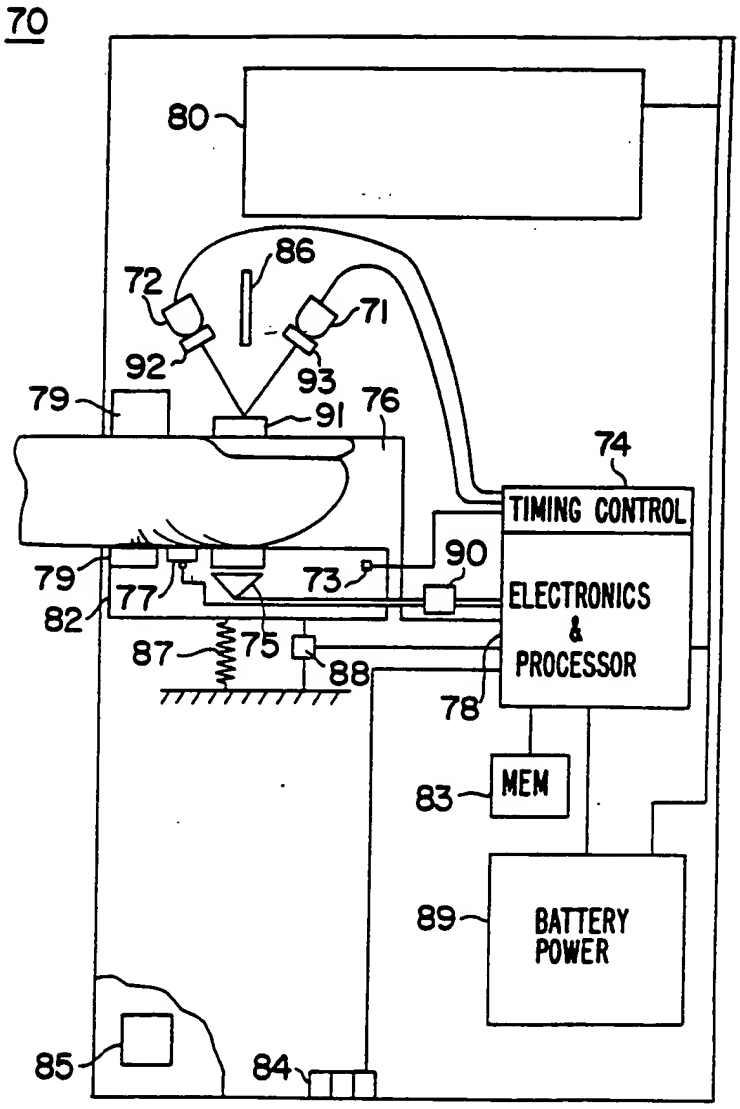

70
80
86
72
71
92
93
79
91
76
74
TIMING CONTROL
90
79
77
73
82
ELECTRONICS
&
PROCESSOR
87
75
88
78
MEM
83
89
BATTERY
POWER
85
84

FIG. 21

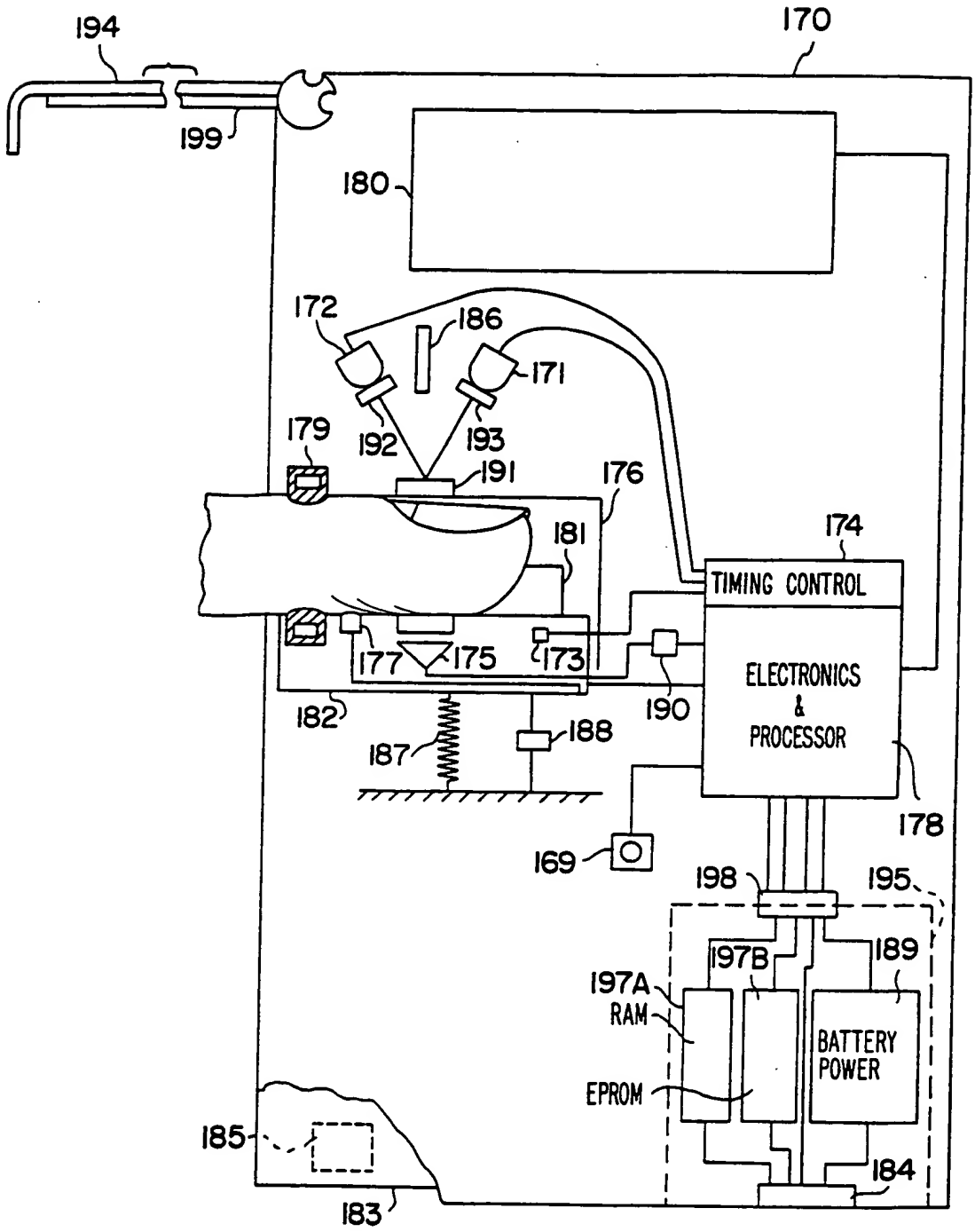

194
170
199
180
172
186
171
179
192
193
191
176
181
174
TIMING CONTROL
ELECTRONICS
&
PROCESSOR
177
175
173
190
182
188
187
178
169
198
195
197B
189
197A
RAM
BATTERY
POWER
EPROM
185
184
183

FIG. 22

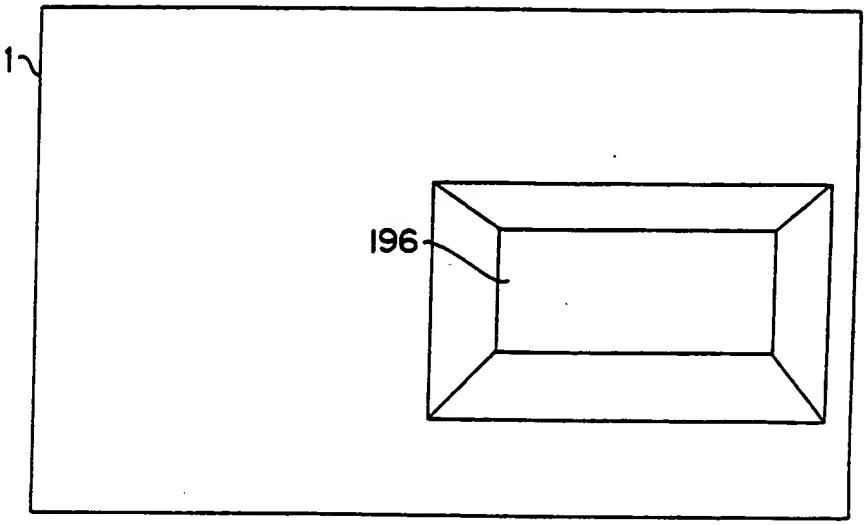


FIG. 23

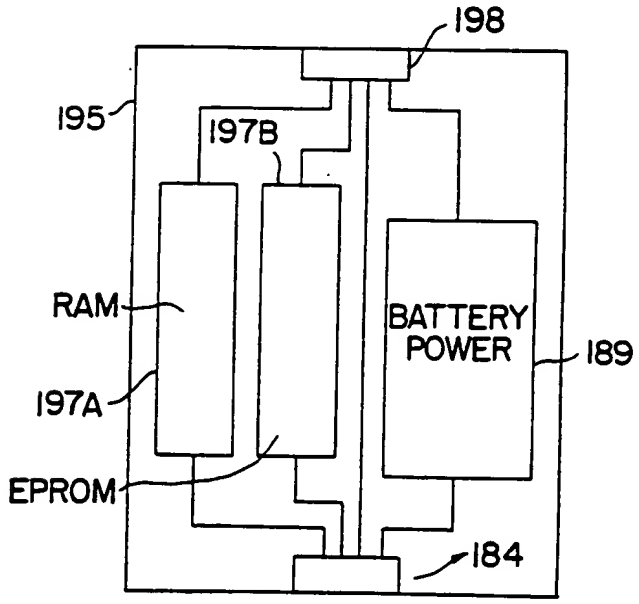


FIG. 24A

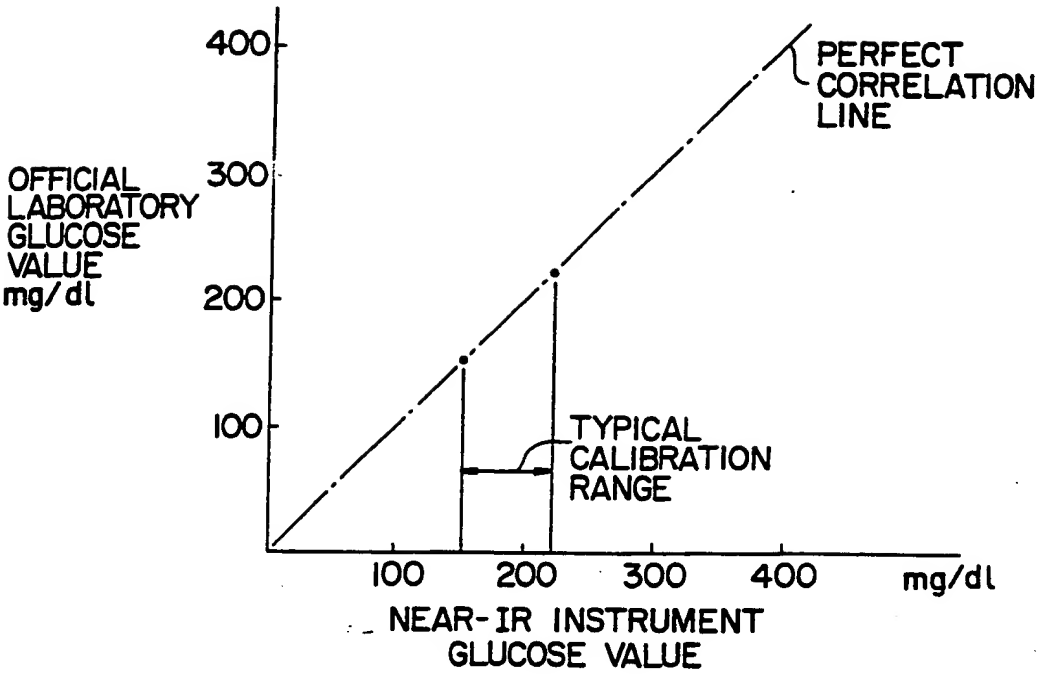


FIG. 24B

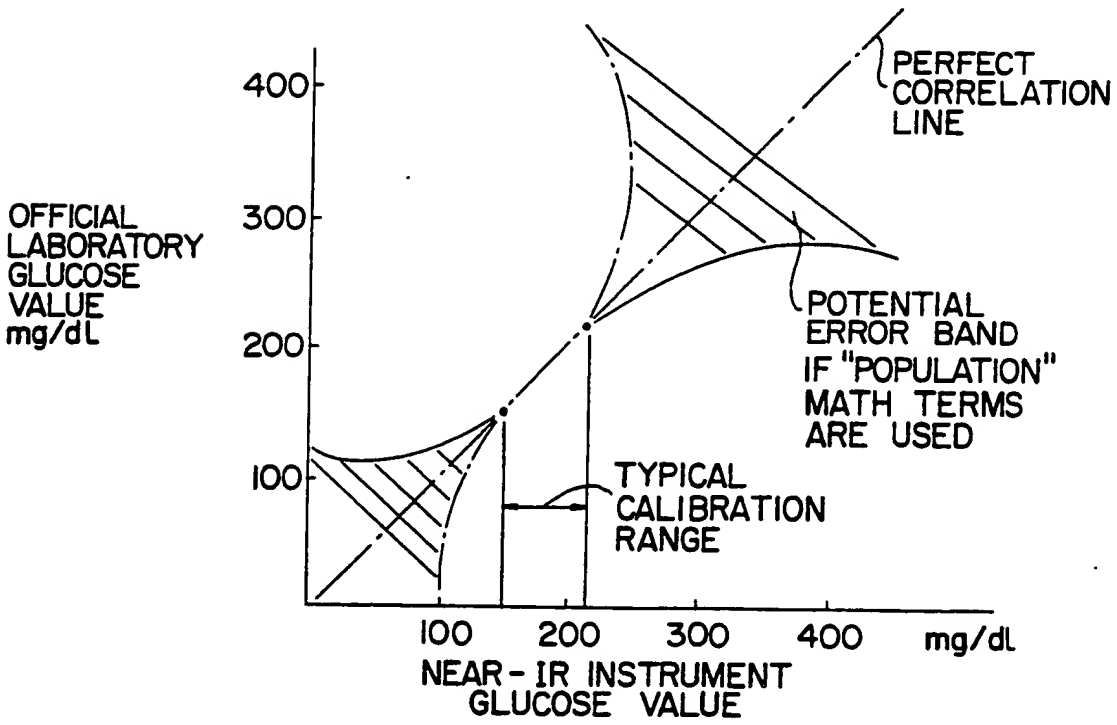


FIG. 24C

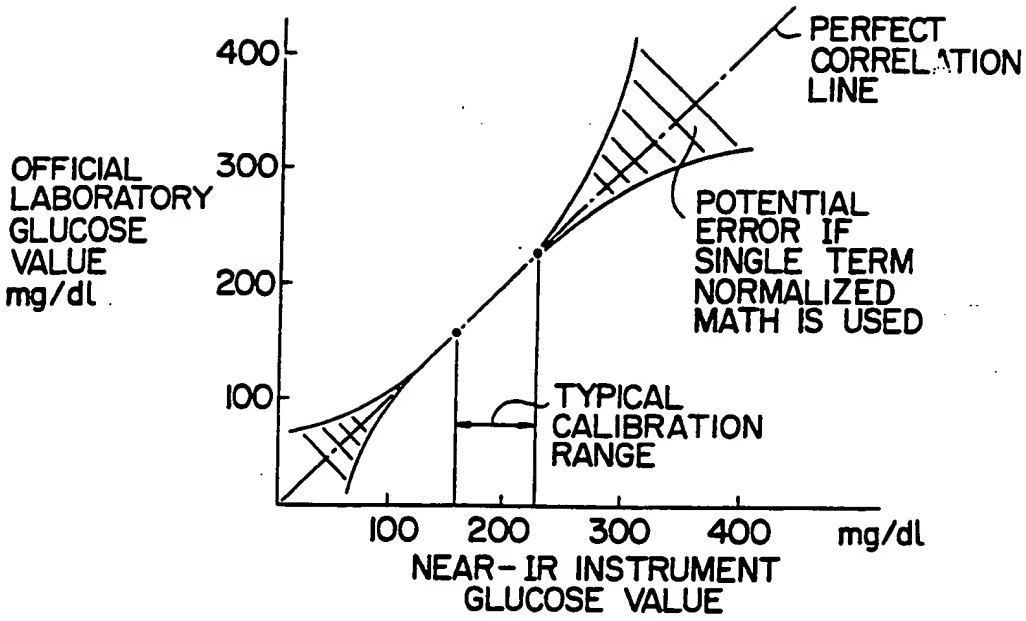


FIG. 24D

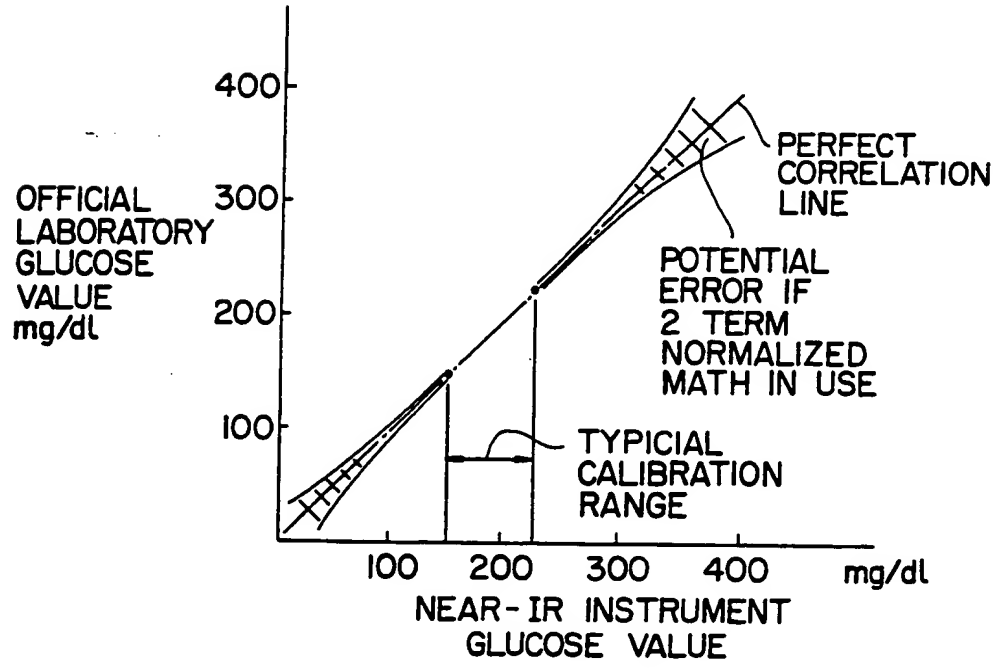
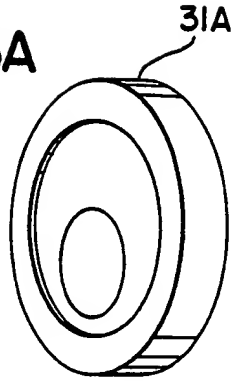


FIG. 25A



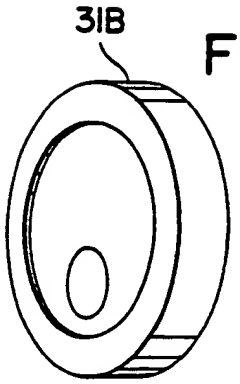


FIG. 25B

FIG. 26

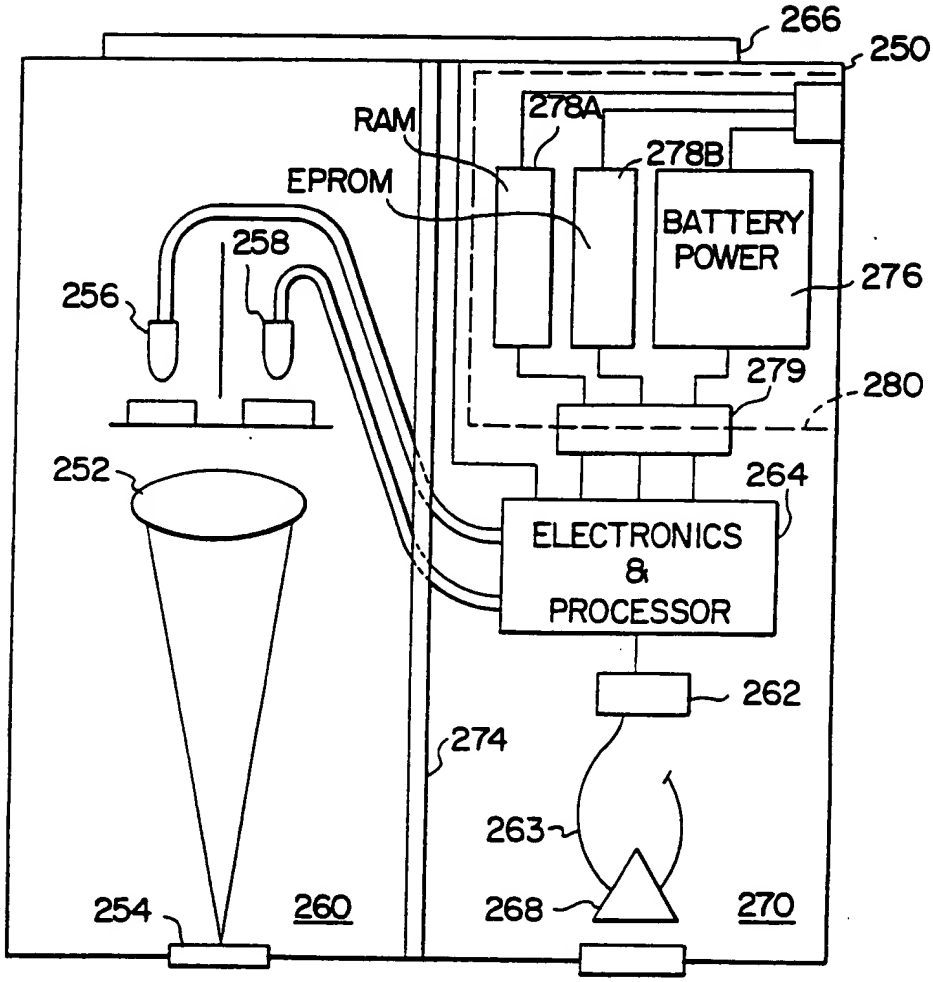


FIG. 27

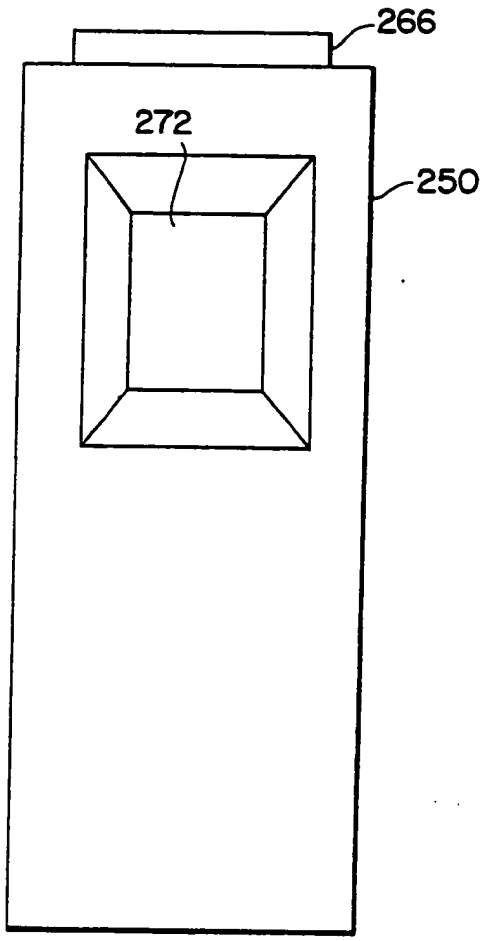


FIG. 28

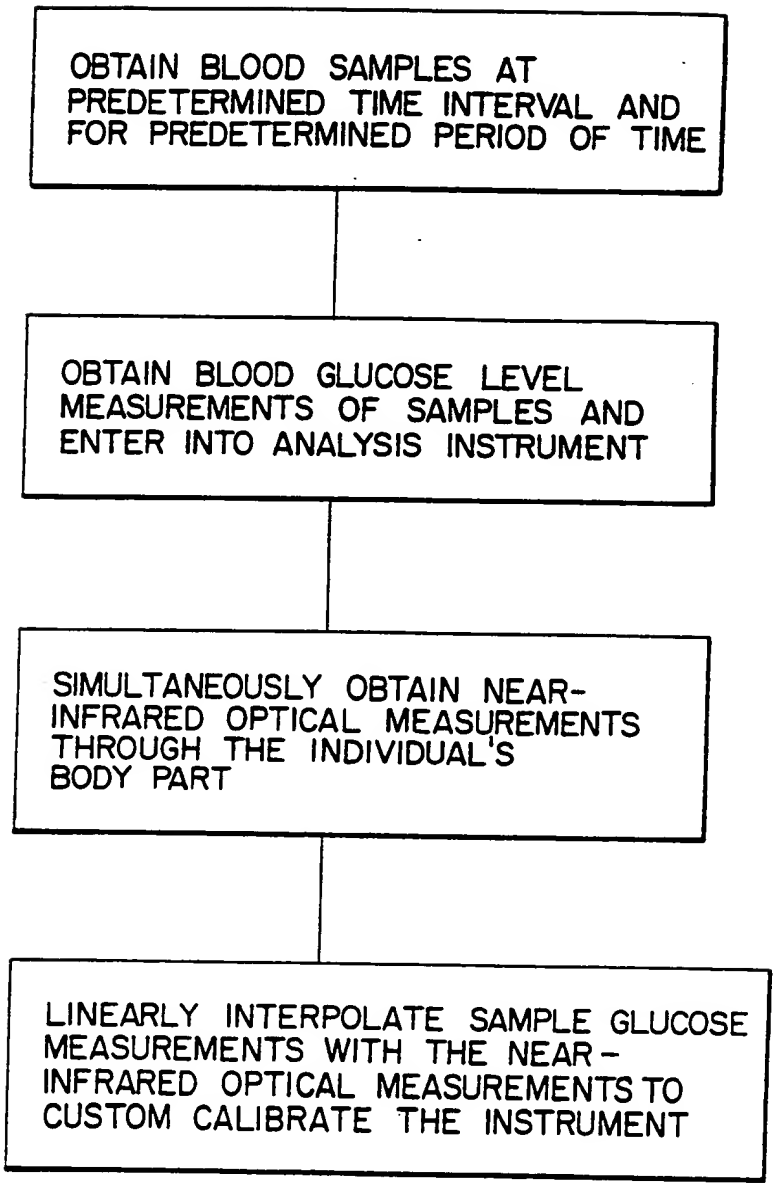

OBTAIN BLOOD SAMPLES AT PREDETERMINED TIME INTERVAL AND FOR PREDETERMINED PERIOD OF TIME
OBTAIN BLOOD GLUCOSE LEVEL MEASUREMENTS OF SAMPLES AND ENTER INTO ANALYSIS INSTRUMENT
SIMULTANEOUSLY OBTAIN NEAR-INFRARED OPTICAL MEASUREMENTS THROUGH THE INDIVIDUAL'S BODY PART
LINEARLY INTERPOLATE SAMPLE GLUCOSE MEASUREMENTS WITH THE NEAR-INFRARED OPTICAL MEASUREMENTS TO CUSTOM CALIBRATE THE INSTRUMENT

FIG. 29

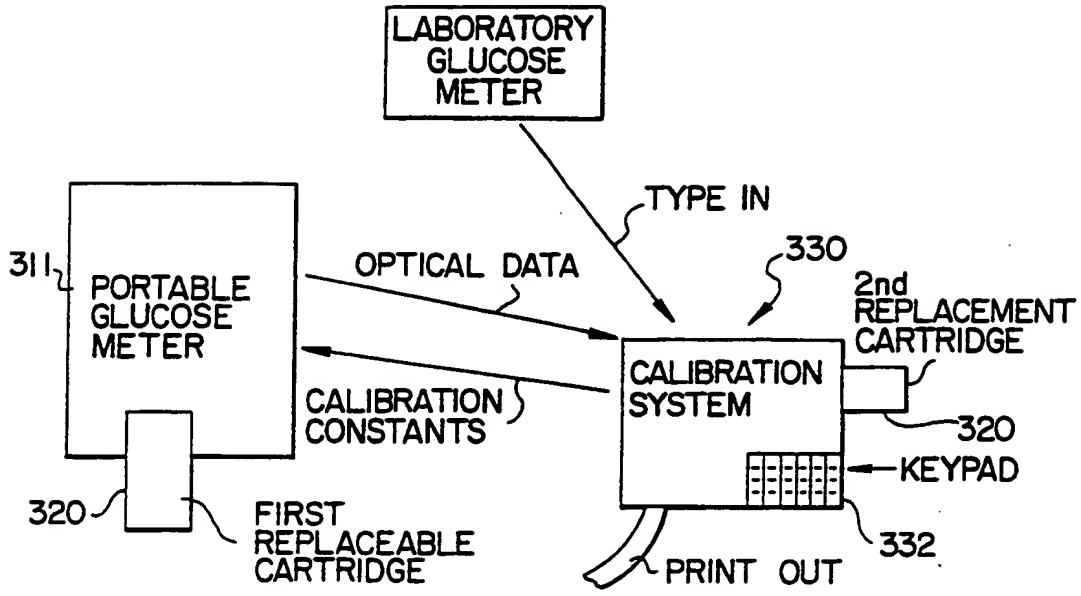

LABORATORY GLUCOSE METER
TYPE IN
311
PORTABLE GLUCOSE METER
OPTICAL DATA
330
2nd REPLACEMENT CARTRIDGE
CALIBRATION SYSTEM
CALIBRATION CONSTANTS
320
KEYPAD
320
FIRST REPLACEABLE CARTRIDGE
332
PRINT OUT

FIG. 30

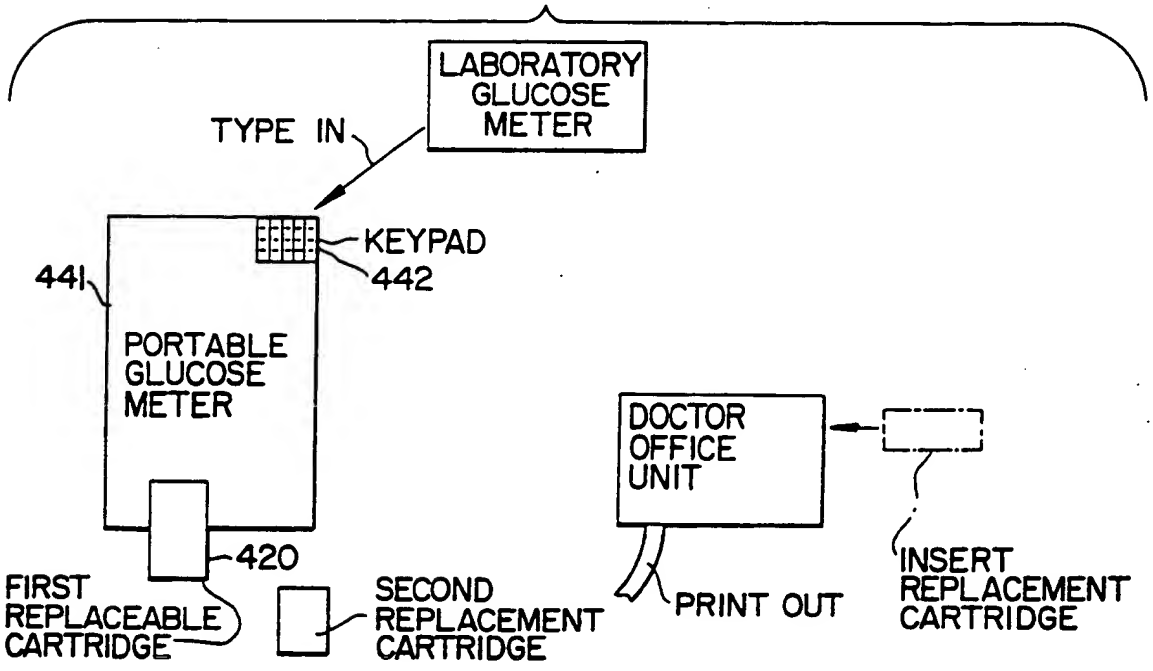
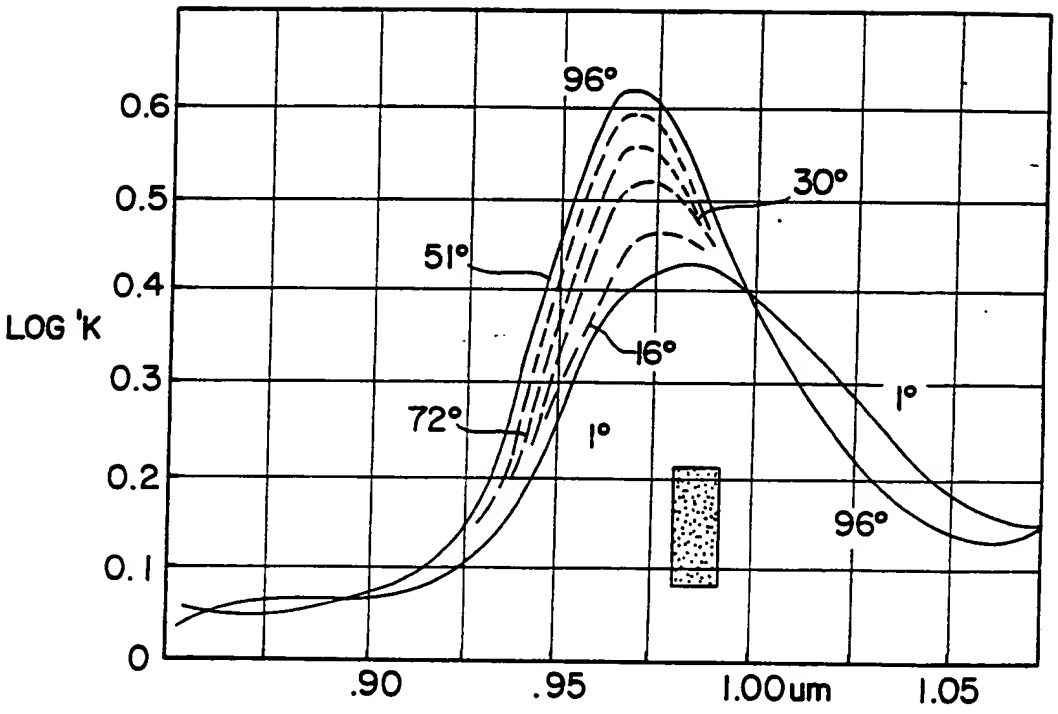

LABORATORY GLUCOSE METER
TYPE IN
KEYPAD
441
442
PORTABLE GLUCOSE METER
DOCTOR OFFICE UNIT
420
FIRST REPLACEABLE CARTRIDGE
SECOND REPLACEMENT CARTRIDGE
PRINT OUT
INSERT REPLACEMENT CARTRIDGE

FIG. 31



INFLUENCE OF TEMPERATURE IN THE VERY-NEAR-IR

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/04616

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): G01N 21/35
US CL.: 250/341,339,343

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
US	250/341,339,343; 356/39; 128/633

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4,882,492 (SCHLAGER) 21 November 1989 See entire document.	1,2,6-16,33-36
Y	US, A, 4,883,953 (KOASHI et al.) 28 November 1989 See entire document.	1,2,6-16,33-36

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
07 OCTOBER 1991	24 OCT 1991
International Searching Authority	**Signature of Authorized Officer**
ISA/US	NGUYEN NGOC-ZO INTERNATIONAL DIVISION for RICHARD HANIG

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